

**UNIVERSITY OF EDINBURGH**

College of Science and Engineering

School of Chemistry

**Synthesis and applications of polymer supported  
peracids**

by

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Thesis for the degree of Doctor of Philosophy

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## ABSTRACT

### Doctor of Philosophy

#### Synthesis and application of polymer supported peracids

*by Gianluca Sechi*

In recent years, an increasing number of solid-phase strategies have been described for high-throughput synthesis of compound libraries. Polymer-assisted solution-phase synthesis has become a prevalent method due to its various advantages over conventional solution-phase chemistry, such as the ease of separation of the supported species from a reaction mixture by filtration and washing, the possibility to use an excess of the reagent to force the reaction to completion and the adaptability to continuous-flow processes. Peroxycarboxylic acids are common oxidants in a wide range of chemical transformations, but their use is often limited due to the associated handling risks. Some relatively stable peracids, such as *meta*-chloroperoxybenzoic acid, are commercially available, but quenching of unreacted species followed by extractions and/or chromatography separation is often required. The immobilisation of this type of reagents on a solid support can offer distinct advantages with respect to handling and stability. Carboxylic ion-exchange resins, with acrylic macroporous matrix, can be oxidised to give highly functionalised supported peroxycarboxylic acids. First, the oxidation of three different carboxylic ion-exchange resins (Amberlite IRP-64<sup>®</sup>, Amberlite IRC-50<sup>®</sup>, Dowex MAC-3<sup>®</sup>) was studied. The oxidation of these resins was performed using hydrogen peroxide at different temperatures, times and acid catalysts. Among the supports and reaction conditions tested, the polymer-supported peracid, generated from Dowex MAC-3<sup>®</sup>, proved to be the best in terms of oxidation capacity. The new high-loading polymer-supported peracid was stable under standard laboratory practice, also after being crushed or heated. Moreover, it was successfully used in the oxidation of sulfides, alkenes, and pyridines, giving the products in high yields and purities without the need for any additional purification step.



## PREFACE

The research described in this thesis was carried out under the supervision of Prof. Mark Bradley at the University of Southampton (Jan. 2004 – Jan. 2005) and at the University of Edinburgh (Feb. 2005 – Apr. 2007).

Part of the work presented here has been published:

- Galaffu, N.; Sechi, G.; Bradley, M., Polymer resin library and the discovery of highly efficient polymer supported reagents and scavengers, *Mol. Diversity*, **2005**, 9, 263-275.

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## ABBREVIATIONS

Ac	acetyl
BEMP	2- <i>tert</i> -butylimino-2-diethylamino-1,3-dimethyl-perhydro-1,3,2-diazaphosphorin
Bn	benzyl
Boc	<i>tert</i> -butyloxycarbonyl
BOP-Cl	<i>N, N'</i> -bis(2-oxo-3-oxazolidinyl)-phosphonic chloride
br	broad
bz	benzoyl
Cbz	carboxybenzyl
d	doublet/day
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	<i>N, N'</i> -dicyclohexylcarbodiimide
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DIC	<i>N, N'</i> -diisopropylcarbodiimide
DIEA	<i>N, N'</i> -diisopropylethylamine
DCM	dichloromethane
DMAP	4-( <i>N, N</i> -dimethylamino)pyridine
DMF	<i>N, N'</i> -dimethylformamide
DMSO	dimethylsulfoxide
DSC	differential scanning calorimetry
<i>ee</i>	enantiomeric excess
EI	electron impact
ELSD	evaporative light scattering detector
equiv	equivalent
ES	electrospray
FRET	fluorescence resonance energy transfer
GC-MS	gas chromatography-mass spectrometry
HATU	<i>O</i> -(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate
HPLC	high performance liquid chromatography
HR	high resolution
IBX	2-iodoxybenzoic acid
IIDQ	2-isobutoxy-1-isobutoxycarbonyl-1,2-dihydroquinoline
IR	infrared spectroscopy
J	coupling constant
LCMS	liquid chromatography – mass spectrometry
LDA	lithium diisopropylamide

m	multiplet (NMR)
MA	methanesulfonic acid
<i>m</i> -CPBA	3-chloroperoxybenzoic acid
MHz	megahertz
Mp	melting point
MS	mass spectrometry/ molecular sieves
m/z	mass/charge ratio
n.a.	not available
NADH	nicotinamide adenine dinucleotide
NMR	nuclear magnetic resonance spectroscopy
<i>p</i>	para
PASP	polymer-assisted solution phase synthesis
PEG	polyethyleneglycol
PMB	<i>p</i> -methoxybenzyl
PS	polystyrene
PTSA	<i>p</i> -toluenesulfonic acid
PyBOP	benzotriazol-1-yloxytri(pyrrolidino)-phosphonium hexafluorophosphate
ROMP	ring opening polymerization
s	singlet (NMR) or strong (IR)
SPE	solid phase extractor
SPOS	solid phase organic synthesis
SPPS	solid-phase peptide synthesis
t	triplet
TBAF	tetra- <i>n</i> -butylammonium fluoride
TBHP	<i>tert</i> -butyl hydro peroxide
TBSCl	<i>tert</i> -butyldimethylsilyl chloride
<i>tert</i>	tertiary
Tf	triflyl / trifluoromethanesulfonyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilyl
t <sub>R</sub>	retention time
UV/VIS	ultraviolet/visible spectroscopy
w	weak

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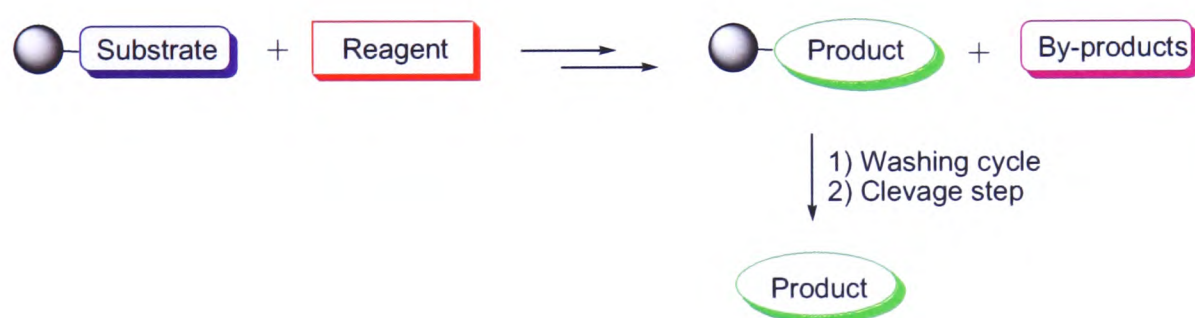
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## 1. Introduction

### 1. 1 Solid phase organic synthesis

The success of a synthetic process is typically correlated with the yield and purity of the final product. Indeed, the real goal in organic synthesis is often not so much to find a reaction or a reagent that carries out the desired chemical transformation, but to find a way to isolate the desired product from a mixture of by-products and unreacted reagents. Under this point of view, a simplified work-up can be considered to be the key of a successful synthesis. The idea of attaching a chemical reagent to an insoluble support that allows rapid product purification, and the ability to drive a reaction to completion through the use of an excess of reagents is highly attractive (Scheme 1.1).

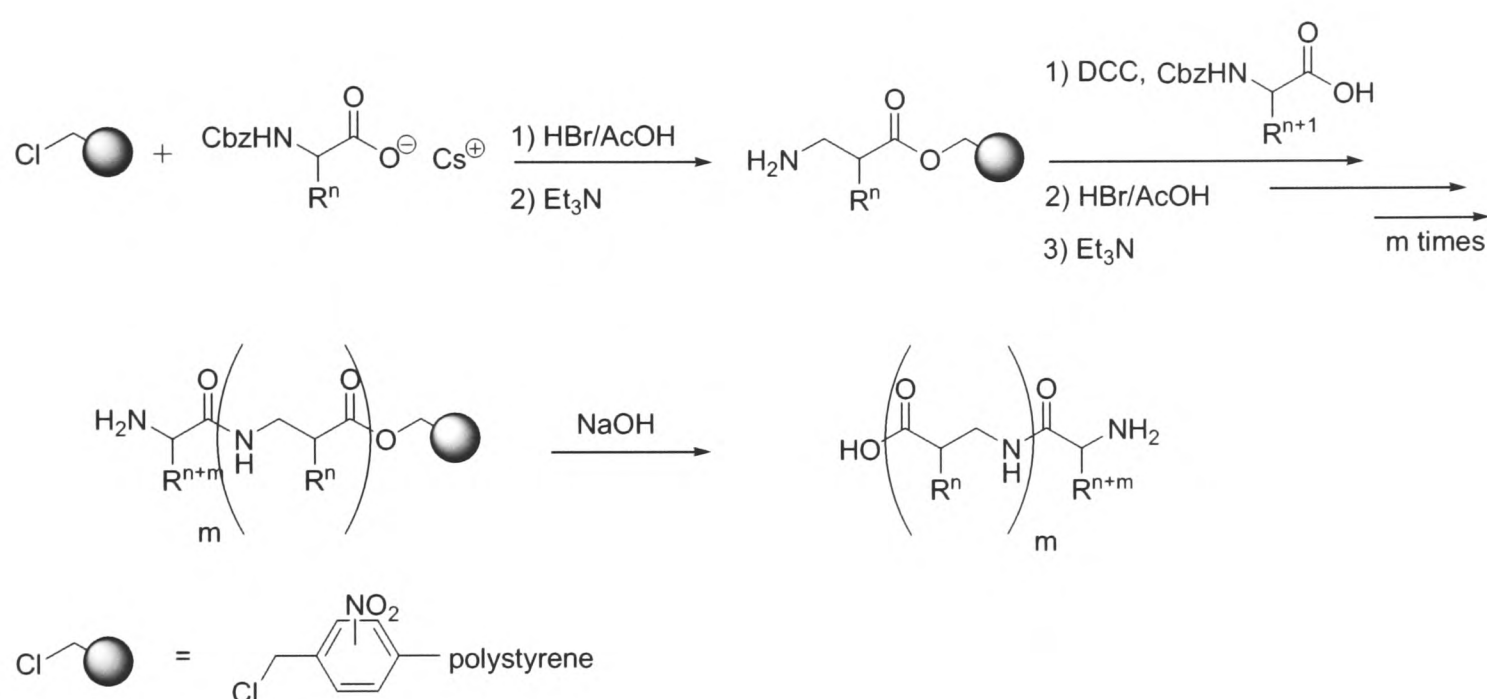


**Scheme 1. 1** General scheme of solid-supported chemistry

In 1955 Du Vigneaud received the Nobel prize in chemistry for the synthesis of oxytocin,<sup>1</sup> which is a polypeptide hormone, and today oxytocin analogues are used to induce and support labour in case of non-progression of parturition. Du Vigneaud can in some respects be considered as one of the pioneers in the development of peptides as drugs. The method originally used for the synthesis of oxytocin was called "solution-or liquid-phase peptide synthesis"; a technique that is complex and relatively tedious because of the necessary isolation, purification and characterization of intermediates at each step of the synthesis.<sup>2</sup> The advent of Merrifield's revolutionary technique in 1963 offered perhaps the first insights into high-throughput synthesis by the transformation of a laborious solution approach to a



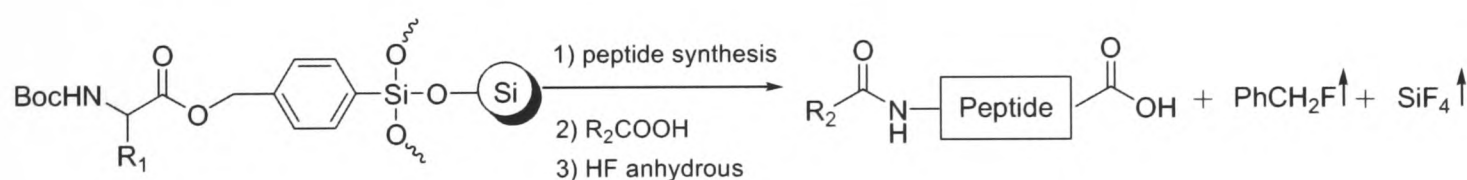
solid-phase variant that took hours rather than weeks to get accomplished. Using this technique,<sup>3, 4</sup> peptide chains could be generated by the consecutive attachment of amino acids onto a growing chain supported on a polymeric support, with purification performed by extensive filtration and washing, and the peptide cleaved once the synthesis was completed (Scheme 1.2). Due to the fact that during the entire process of synthesis the growing peptide is always anchored onto the support, Merrifield called this procedure solid-phase peptide synthesis (SPPS).



**Scheme 1. 2** Merrifield's general method for solid-phase peptides synthesis

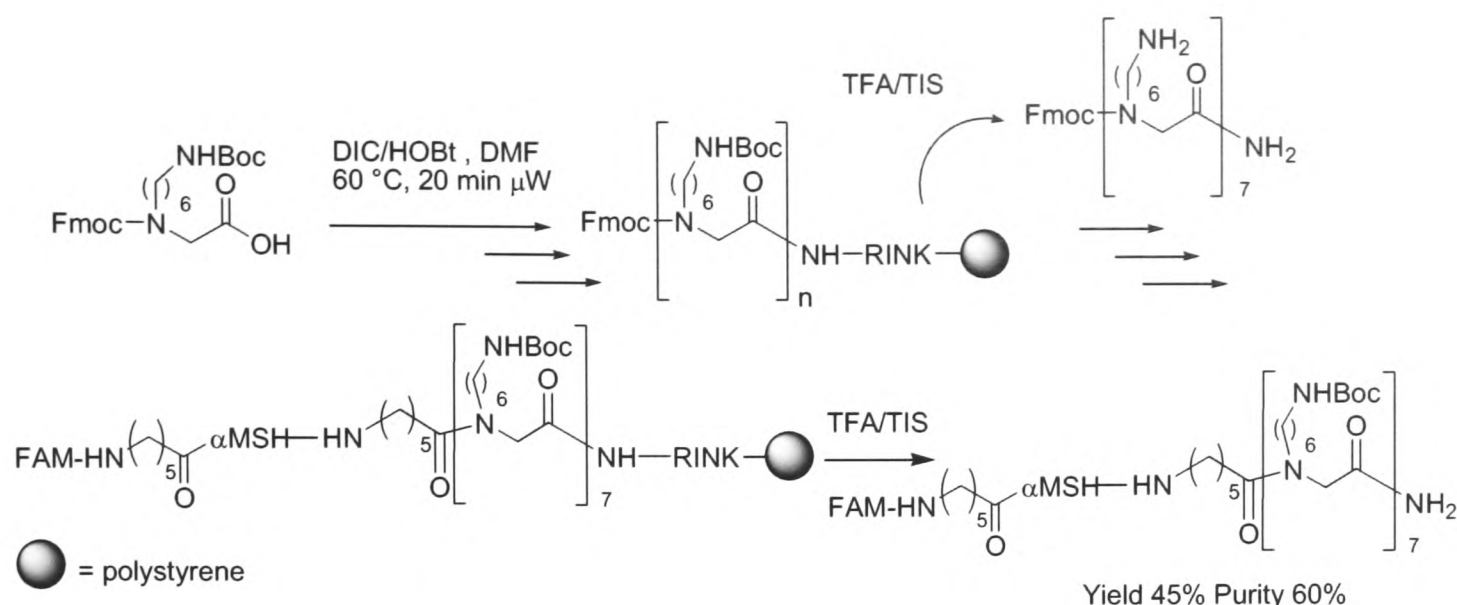
The method soon proved to be extremely powerful, and the synthesis of relatively complicated peptides, and even small proteins such as ribonuclease A<sup>5</sup> and ribonuclease S,<sup>6</sup> was demonstrated. The solid-phase peptide synthesis method was initially criticised, due to the fact that it was not possible to isolate and purify the intermediates.<sup>7</sup> However, the introduction of analytical and preparative HPLC methods by Horváth<sup>8</sup> dramatically enhanced the usefulness of the method. Furthermore, the method was quickly applied by the development of automated instruments,<sup>9, 10</sup> so that the technology for the rapid discovery of new peptides became accessible to the research community. In 1984 Geysen<sup>11</sup> demonstrated how hundreds of different peptides could be generated in a few steps, using an innovative procedure in conjunction with the technique reported by Merrifield. Geysen modified

the methodology using small plastic pins, instead of beads, which were immersed in a 96-well plate containing defined aminoacids. Varying the amino acid in each well of the plate allowed the variation of the peptide sequence attached onto each pin. Several years later, Houghten<sup>12</sup> introduced a method that, instead of plastic pins, used porous bags containing resin beads, increasing in this way the amount of final products obtained. Furka,<sup>13</sup> in 1988, reported a procedure where the number of peptides could be exponentially increased by simply splitting and mixing the beads pool. This gave rise to the well-known one-bead-one-compound concept,<sup>14</sup> where millions of peptides could be produced and screened directly by on-bead enzyme assay methodology.<sup>15</sup> Although solid phase synthesis of peptides is today a well established technique, new and innovative approaches appeared over the past few years. In particular, Houghten<sup>16</sup> developed "volatilizable" supports for the high-throughput synthesis of peptides. In this approach, silica gel was functionalised initially using a volatilizable linker before being used for traditional solid-phase synthesis of peptides. Treatment with hydrofluoric acid caused both the linker and support ( $\text{SiF}_4$ ) to become volatile with the remaining residue being the desired peptide (Scheme 1.3).



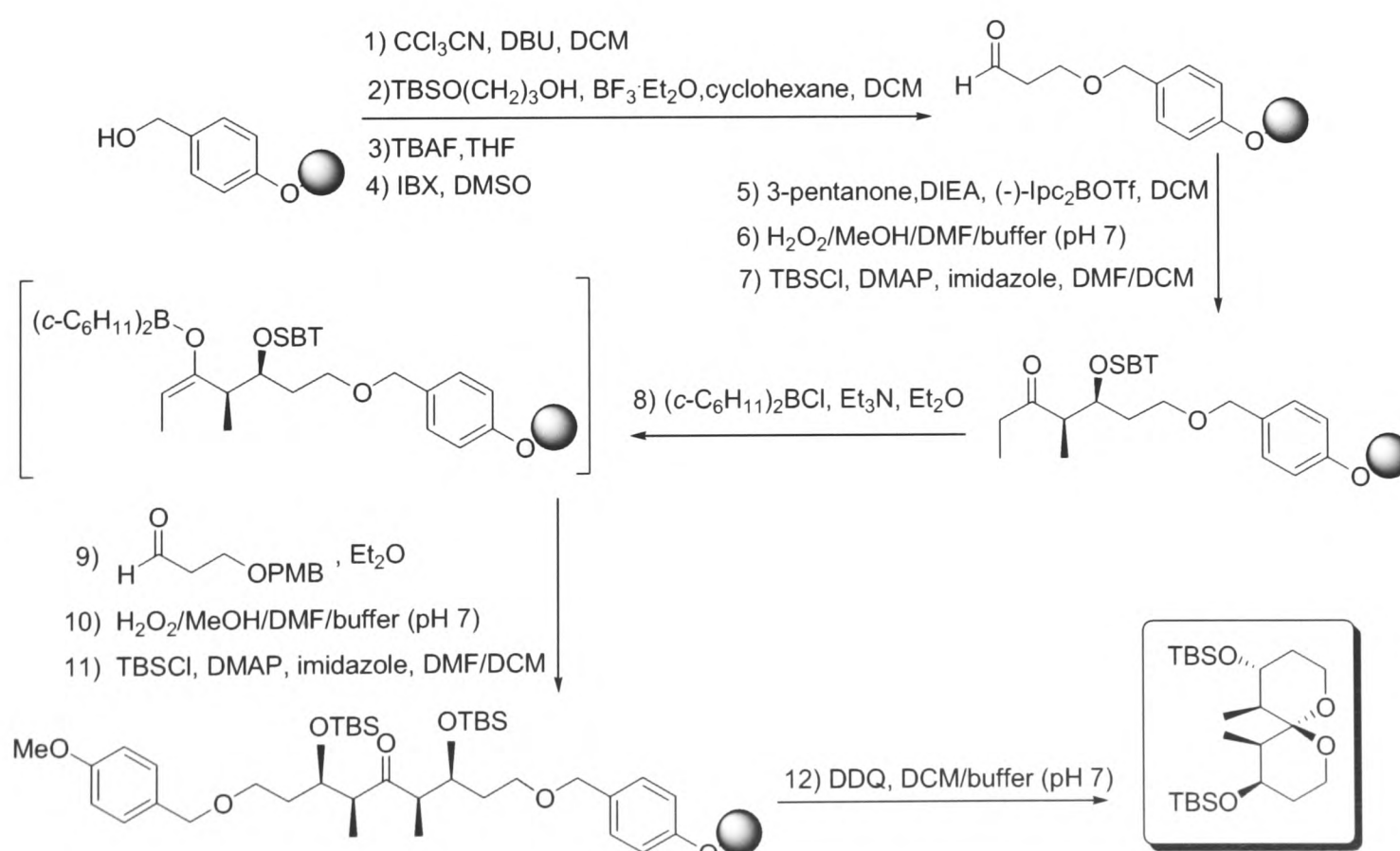
**Scheme 1. 3** General synthesis of *N*-protected peptides on a "volatilizable" support

More recent innovations are the application of relatively new technologies, such as microwave irradiation, in order to reduce the reaction time needed to achieve difficult peptide couplings.<sup>17, 18</sup> Recently, Fara<sup>19</sup> has reported the microwave mediated synthesis of fluorescence resonance energy transfer (FRET)-peptides using *N,N'*-di-isopropylcarbodiimide/1-Hydroxybenzotriazole, as coupling promoters, under microwave irradiation with purities of >90% (Scheme 1.4).



**Scheme 1. 4** Solid-phase synthesis of a dye labelled peptide ( $\alpha$ -MSH) conjugated to a heptapeptide

Solid-phase synthesis has not only revolutionised peptide synthesis, but the past years have seen an increasing interest in this methodology for the successful development of compound libraries of difficult natural product structures,<sup>20, 21</sup> (Scheme 1.5). For example, the solid-phase synthesis of 6,6-spiroketal proceeded in 12 linear steps and provided access to the desired compound by a stereoselective aldol reaction of boron enolates as a key stereo-differentiating transformation.



**Scheme 1. 5** Solid phase synthesis of 6,6-spiroketal

## 1. 2 Supports for solid-phase chemistry

The term solid support is generally used to denote the insoluble material upon which reactions are performed. The reactions are not carried out only on the surface but also within the support. The main characteristic of those supports is their insolubility, which allows easy separation from the reaction mixture by filtration. A large variety of polymeric supports have been developed in the last fifty years in order to address various issues related to the evolution of solid phase organic chemistry. There are two main approaches for the preparation of functionalised polymers. One approach involves the polymerisation of monomers which carry the desired functionality; the second is the chemical modification of a pre-formed polymeric backbone. Many functionalised polymers are now becoming commercially available, making their use quicker, simpler and more practical. Some of the desired characteristics a polymer support must have are:

- Size and shape of the particles should be varied quite easily in order to be adapted to various situations of handling and filtration.
- The polymer has to be inert to chemical and physical stress such as strong acidic or basic conditions, presence of radicals, oxidising and reducing conditions and drastic variation of temperature and pressure.
- Limited swelling in the solvents used in the reaction, and good interaction of the homogeneous reagents with the functionalities within the polymeric matrix.
- Easy surface modification, in order to allow the introduction of different functional groups suitable for the desired chemical transformation.

The kinetics of a reaction on solid phase organic synthesis is strongly connected to the diffusion rate of the reagents within the polymeric network. To obtain optimal reaction rates, steric and diffusion barriers must be minimised. However, as mechanical and chemical stability cannot be sacrificed, a compromise between well-solvated gel supports with low level of cross-linking and porous but rigid materials with high level of cross-linking need to be found.

---

A classification of solid supports,<sup>22</sup> based on physical properties, has been proposed:

- **Gel-type supports.** Which are the most common inert supports in solid phase chemistry with a homogeneous distribution of functional groups within the polymer network.
- **Surface-type supports.** As the name describes, these inert materials are mainly surface functionalised, examples include cellulose,<sup>23</sup> controlled pore glass<sup>24</sup> and silica.<sup>16</sup>
- **Composites and supported gels.** Which are composed of a gel-type surface, supported on a rigid matrix in order to improve the global mechanical stability. An early example is the preparation of structured and functional polymer grafts on diamond surfaces,<sup>25</sup> where the stable covalent bonding between the shell and the core allows reactions to be conducted in relatively drastic conditions without a noticeable detachment of the polymeric coating. Thus, various functionalities, such as nitro, sulfonic, and aminomethyl groups have been successfully incorporated into these composite materials.
- **Brush polymers** have multiple linear branches densely linked to a polymeric backbone.<sup>26, 27</sup> Typically, brush polymers adopt a spherical conformation and the backbone is shorter compared to the brushes, whereas, as the backbone becomes longer and comparable in length to the brushes, the steric hindrance among these stiffen the backbone and forces the brush polymers to adopt a cylindrical conformation.<sup>28</sup>

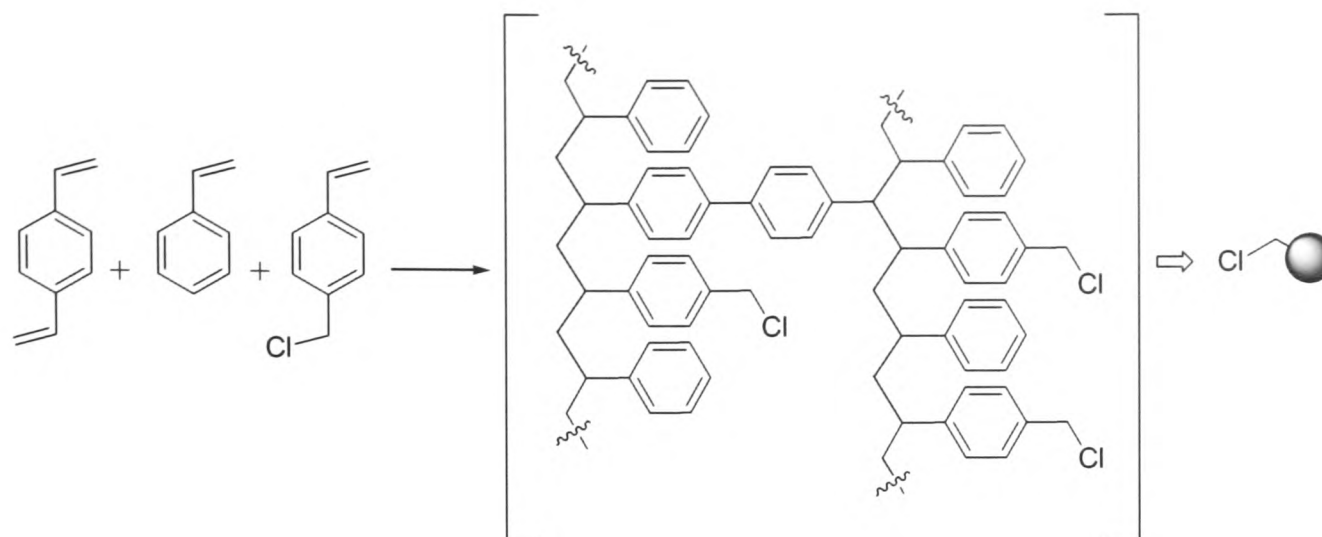
### 1.2. 1 Polystyrene based materials

These materials are usually synthesised by radical polymerisation of styrene and divinylbenzene (DVB).<sup>29</sup> The product obtained is a hydrophobic material in the form of spherical beads that are solvated by non-polar solvents such as toluene and dichloromethane. The faculty of the solvent to swell or shrink the polymeric matrix can increase the ability of reagents to diffuse within the beads and dramatically influence reaction rates. The physical and chemical properties of the beads are deeply connected to the percentage of divinylbenzene used as a cross-linker.<sup>30</sup> High levels of

cross-linking produce more robust supports, therefore, drastic reaction conditions such as harsh mechanical stirring at high temperatures are allowed. On the other hand slow reaction rates are often observed due to the fact that the reagents cannot easily diffuse within the polymeric network.<sup>31</sup> On the contrary, low levels of cross-linking produce highly swellable beads that exhibit better reaction kinetics but are more fragile. Another important issue to be considered is the loading in functional groups, as when the functional groups are too close electrostatic and/or steric effects can occur. Often spacers between the polymer and the reactive functionality of the resin can be placed in order to keep the functionality far from the support, thus reducing the interactions between the molecules in solution and the polymer matrix.<sup>32</sup> Generally, the loading and application of polystyrene resins can be grouped in the following ways:

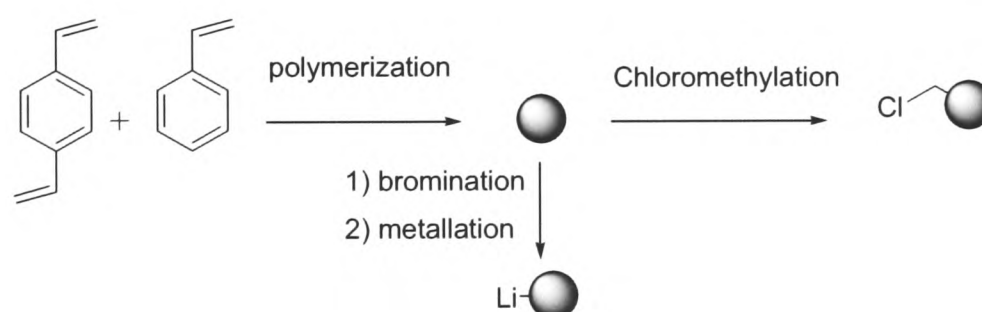
- < 0.1 mmol/g suitable for solid phase oligonucleotide synthesis and the synthesis of large peptides/proteins.
- 0.1-0.7 mmol/g, suitable for supported catalysts.
- 0.5-1.5 mmol/g suitable for solid phase synthesis (small molecules and peptides) avoiding problems of steric hindrance.
- > 2 mmol/g preferred for scavenger and reagent based resins, as these types of reagents are added in excess.

The functionalisation of the resin can be achieved by adding monomers with the desired functional groups into the polymerisation mixture. The amount of active sites can be controlled from the ratio among the monomers. In this approach the functionalities are randomly distributed in the final product. Moreover polymers with functional groups situated in sterically unfavourable position can be prepared (for example where a functional group is attached to the less unfavourable position in the phenyl ring) (Scheme 1.6).



**Scheme 1. 6** Preparation of chloromethylpolystyrene resin

An alternative to the pre-functionalisation is the derivatisation of polymeric support after copolymerisation. In particular, polystyrene based resins can be functionalised by electrophilic aromatic substitution in the presence of a Lewis acid,<sup>33</sup> or by metallation of a brominated resin<sup>34</sup> (Scheme 1.7).



**Scheme 1. 7** Derivatisation of a polymeric matrix

This method is not problem free; in fact, an additional level of cross-linking during the post functionalisation (for example chlorometylation or sulfonation), due to the methylene or sulfone bridge, can occur.

### 1. 3 Limitations of solid phase organic synthesis

Despite all these remarkably achievements in the rapid synthesis of thousands of compounds and the discovery of new ones, the development of a new solid phase synthesis often face some inherent difficulties correlated with the nature of the insoluble support:



- the compatibility of intermediates and reagents involved in the synthesis with the polymeric support and the solvent required for their swelling;
- all reactive sites on the support need to react to avoid the formation of by-products;
- two extra steps in the protocol, the attachment to the support and subsequent cleavage of the final product are necessary;
- reaction monitoring and temperature control of the products attached to the beads.

These limitations in solid-phase organic synthesis have encouraged the development of another area of supported chemistry known as polymer-assisted solution-phase synthesis (PASP).

#### 1. 4 Polymer-assisted solution-phase synthesis

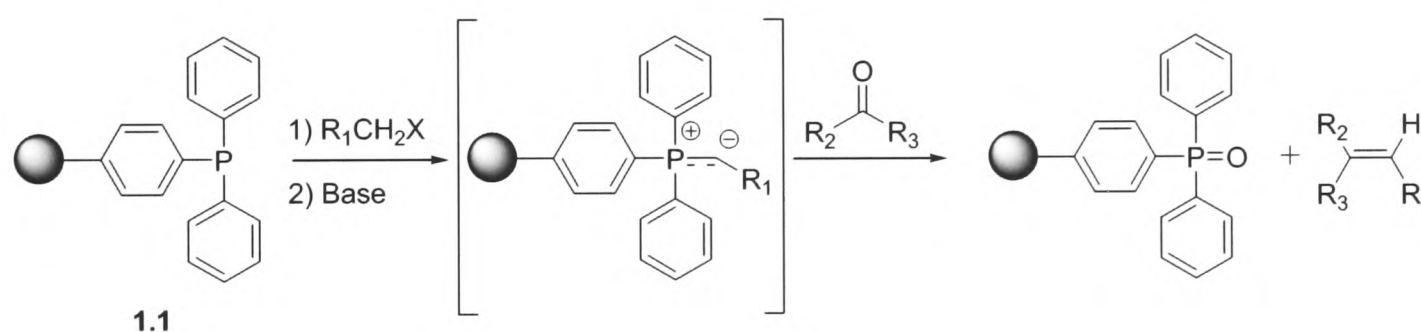
Since the pioneering work by Merrifield,<sup>35</sup> and the introduction of the "solid-phase technique" for the synthesis of peptides, polymeric supports have become the subject of considerable interest as insoluble matrices in organic synthesis. However, despite all the achievements this technique has recorded over the last 60 years,<sup>36</sup> not all the limitations of this method in comparison to solution phase techniques have been overcome. An alternative approach to circumvent some of these drawbacks involves the use of a technique termed polymer-assisted solution-phase synthesis, where the substrate is not attached to the support and all chemical transformations take place in solution (Scheme 1.8).



**Scheme 1. 8** General scheme for reaction mediated by polymer-supported reagents

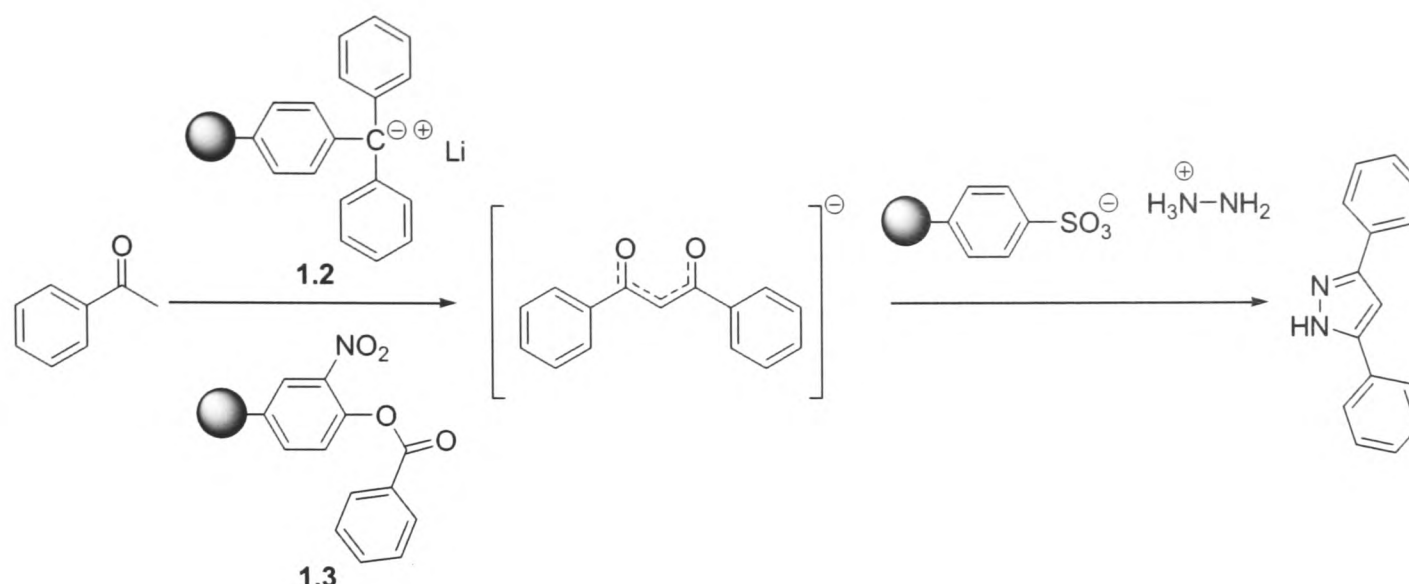


Polymer assisted solution phase synthesis reduces the need for purification and allows reactions to be driven to completion through the use of excess of reagents.<sup>37</sup> Furthermore, reaction progress can conveniently be monitored by standard solution-phase techniques (TLC, LC/MS, *etc.*), thereby minimising the time required to optimise a transformation. A wide variety of immobilised reagents and scavengers have been developed over recent years and an ever increasing number have become commercially available.<sup>38</sup> The use of a reagent immobilised on a polymeric support was firstly reported by Sussman in 1946,<sup>39</sup> but only in the early 1970s and 1980s it was popularised by the groups of Cainelli,<sup>40</sup> Leznoff,<sup>41</sup> Sherrington<sup>42</sup> and Hodge,<sup>43</sup> who were involved in the development and application of polymer-supported reactive species, and the revolutionary potential of these materials became clear. A wide variety of supported reagents were investigated; one of the first examples being the use of a triphenylphosphine polymeric derivative **1.1** for the Wittig reaction (Scheme 1.9).<sup>44</sup>



**Scheme 1. 9** Wittig reaction using polystyrene analogues of triphenylphosphine

Cohen<sup>45</sup> reported that two species, that were not compatible in solution, could be used at the same time if immobilised (Scheme 1.10). For instance the supported version of a trityl lithium **1.2** and an activated ester **1.3** were used in the synthesis of a diketone. The authors described this procedure as the "wolf and the lamb" reaction.



**Scheme 1.10** An example of a "wolf and lamb" reaction

Despite the increasing number of publications on polymer-supported organic chemistry,<sup>42</sup> industrial scientists and core academic synthetic chemists were sceptical to this "new" technology. Only during the 1990s, with the advent of two important transformations in industrial strategy, the interests and financing of supported chemistry raised:<sup>46</sup>

- ✓ The first of these changes was the development of high throughput screening (HTS) and its need of large amounts of products (10-100 mg) of high purity (> 90%) in focused libraries.
- ✓ The second was the incoming of new regulations requiring more efficient chemical processes with a lower environmental impact.<sup>47</sup>

Polymer-assisted solution-phase synthesis, due to the advantages offer in terms of automation and robotics, is today a well used tool in parallel synthesis. Compared to solid phase synthesis, a protocol that involve the use of polymer supported reactive species can be rapidly optimised as an alternative to pre-existing solution phase methodologies, with a noticeable reduction in time during the purification. In terms of environmentally friendly industrial processes, bonding a hazardous chemical to an insoluble support can reduce the risks involved in handling and disposal.

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A list of the reasons why this technique is attractive is given below:

- Monitoring and temperature control can be performed by traditional methods due to the fact that substrates stay in solution.
- Reactions are driven to completion using an excess of supported reagents or the sequestering of the reagent in solution by a complementary functionalised polymer.
- Pure products are obtained after a simple filtration and removal of solvent.
- Supported catalysts can be easily handled and regenerated.
- Supported reagents shown reduced toxicity compared to non-supported analogous.
- Multi-step synthesis can be achieved in a single reactor. Due to the site isolation principle, different polymer-supported reagents can be used simultaneously.
- Automated synthesis and purification including flow systems and microreactors can be easily adapted.

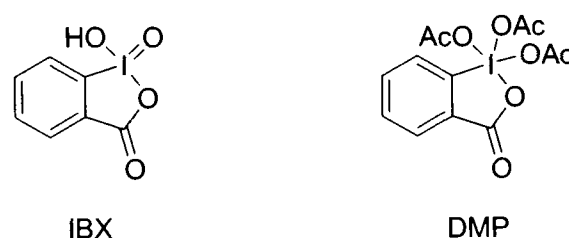
The power of polymer-assisted solution-phase synthesis is today well-demonstrated from the number of publications and commercially available materials. Because of the breadth of this area and its expansion over the last 20 years, several different methodologies involved will be discussed below.

#### **1.4. 1 Polymer-supported reagents**

Polymer supported reagents allow chemical transformation of the substrate present in solution to be carried on without the needing of tedious purification steps. An excess of reagent can be used to conveniently drive a reaction to completion, and the reactions are easily monitored using the well-established methods available for soluble species (Scheme 1.8).<sup>48</sup> The number of reactions where a supported-reagent could be used is continuously increasing; their use for oxidations, reductions, halogenations, coupling reactions, nucleophilic substitutions and deprotonation is well documented in several reviews.<sup>36, 38, 49-51</sup>

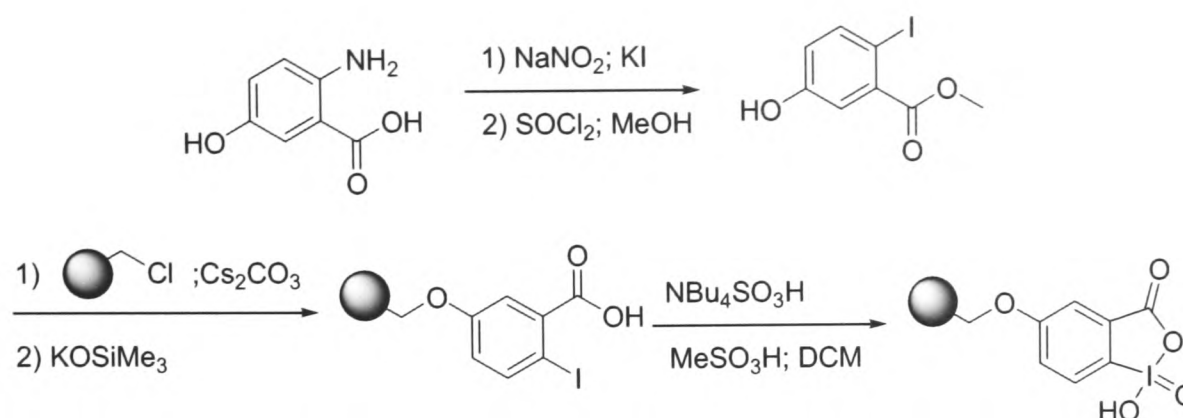
Some of the most known examples are discussed below:

- **Oxidations:** over the last few years polyvalent organo iodine reagents have been demonstrated to be versatile selective oxidising agents, highly chemoselective, combined with their benign environmental character.<sup>52</sup> The most important representative of pentavalent iodine heterocycles is 2-iodoxybenzoic acid (IBX), but its safety issues under excessive heating or impact<sup>53</sup> and insolubility in most organic solvents have limited its wide applications. In 1983 Dess and Martin transformed IBX to the soluble 1,1,1-tris(acetyloxy)-1,1-dihydro-1,2-benziodoxol-3-(1*H*)-one, which is commonly known as Dess-Martin periodinane (DMP), by heating IBX with acetic anhydride at 100 °C (Figure 1.1).<sup>54</sup>



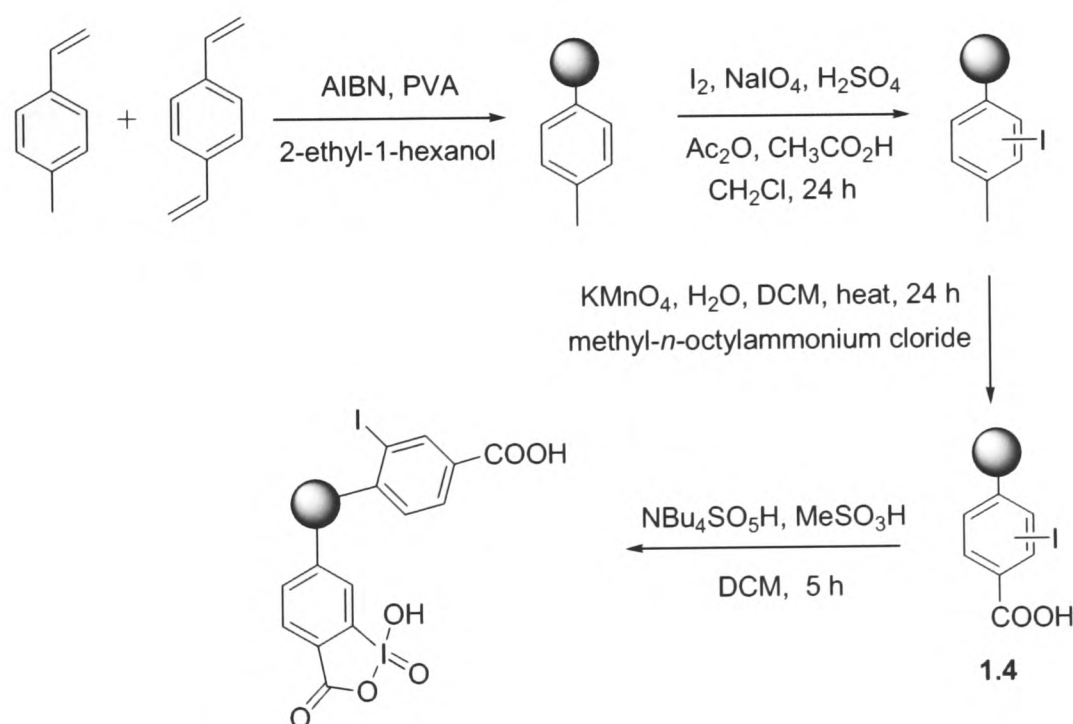
**Figure 1. 1** Structures of IBX and DMP

Various groups have reported the immobilisation of IBX onto solid and soluble supports, leading to a non-explosive IBX variant, compatible with solvents such as THF and dichloromethane.<sup>55</sup> Methods to prepare 2-iodobenzoic acid resins have been reported in the past years,<sup>56, 57</sup> and commercially available IBX resin is prepared following the method shown in Scheme 1.11. Rademann's<sup>58</sup> method involves the coupling of 2-iodo-5-hydroxybenzoic acid onto a polystyrene based support. After a subsequent activation step, the supported IBX reagents were able to carry out the fast and efficient conversion of alcohols into aldehydes or ketones.



**Scheme 1.11** Rademann's synthesis of polymer-supported IBX reagent

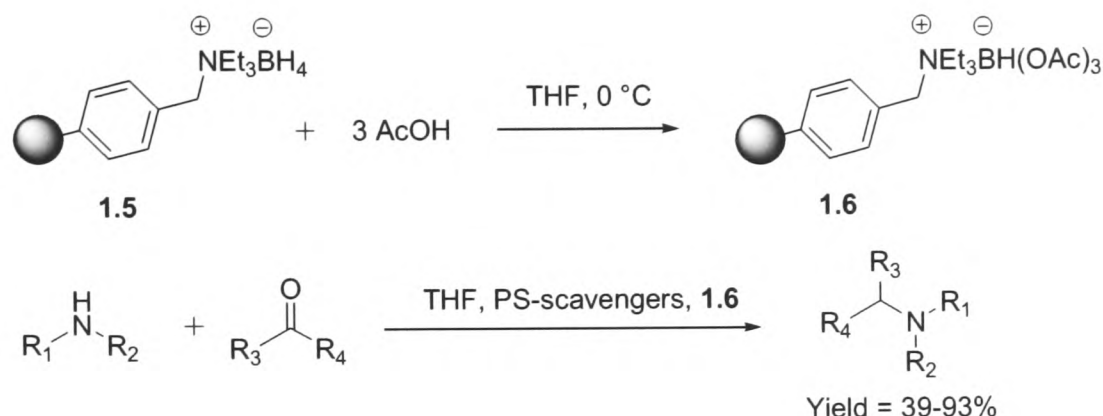
Sutherland used a fundamentally different approach which relied on the introduction of the iodobenzoic acid moiety **1.4** directly on the resin backbone (Scheme 1.12).<sup>59</sup>



**Scheme 1.12** Sutherland's synthesis of polymer-supported IBX reagent

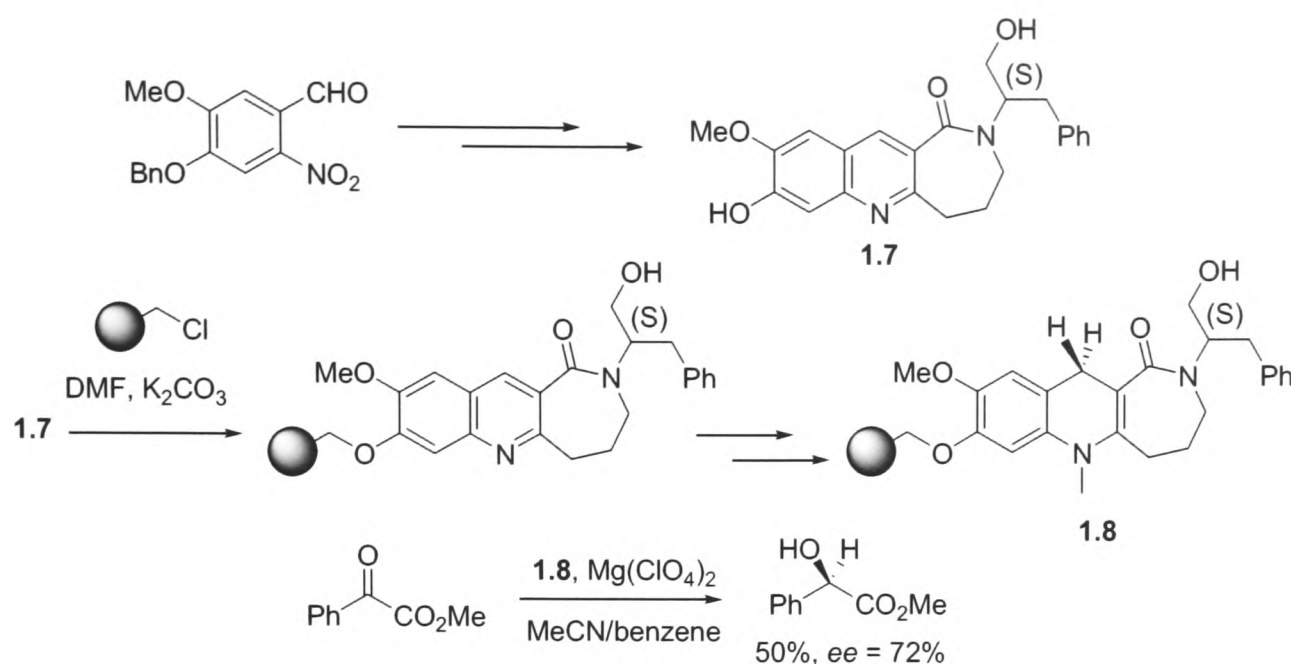
- **Reductions:** the reductive amination of carbonyl compounds provides convenient access to different amines and has wide applications in synthetic organic chemistry.<sup>60</sup> Several kinds of polymer-supported borohydride-based reducing reagents have been developed for this reaction. For example the synthesis of polymer-supported triacetoxyborohydride from a commercially

available macroporous triethyl-ammonium methylpolystyrene borohydride resin **1.5** is well known.<sup>61</sup> The supported reducing reagent was successfully used in the synthesis of secondary and tertiary amines by reductive amination under mild conditions (Scheme 1.13).



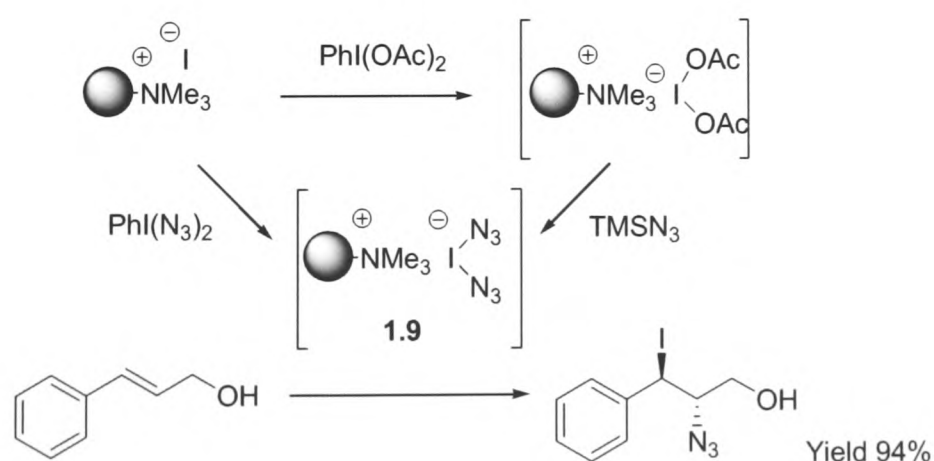
**Scheme 1. 13** Synthesis and application of polymer-supported triacetoxyborohydride reagent

Reactions were carried out with the carbonyl compound as the limiting reagent and the addition of a polymer-supported scavenger. Supported benzaldehyde or isocyanate were used to selectively remove excess of amines. Another example is the use of polymer-supported chiral nicotinamide adenine dinucleotide hydrogenated (NADH) model derived from quinoline, which has showed enantioselectivity in the reduction of methyl benzoylformate.<sup>62</sup> The supported reagent **1.8** was synthesised by bonding the phenol compound **1.7** via reaction with chloromethylated polystyrene followed by reduction of the quinoline ring (Scheme 1.14). Polymer-supported reagent **1.8** was tested in the asymmetric reduction of methyl benzoylformate in the presence of magnesium perchlorate.



**Scheme 1. 14** Synthesis and application of polymer supported NADH model

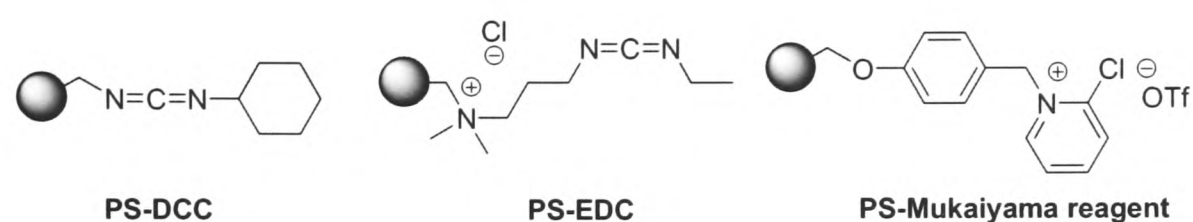
**Halogenations:** halogenation of organic compounds is a crucial step in the preparation of various synthetic intermediates or products. Therefore, it is not surprising that several polymer-bound halogenation reagents have been developed since the early days of polymer-supported reagents. Most of these reagents are based on ion-exchange resins often loaded with halogenated counterions.<sup>51</sup> These highly reactive reagents have proven to be stable and easily handled materials that can conveniently be stored. For example, polymer-supported diazidoiodate (I) reagent **1.9** is a stable and non explosive source for iodine azide, which proves that separation of active sites on polymeric supports occur.<sup>63</sup> The reagent was employed in the azidoiodination of alkenes under very mild conditions with easy product isolation (Scheme 1.15).



**Scheme 1. 15** Preparation of polymer-bound iodine azide **1.3** and its application

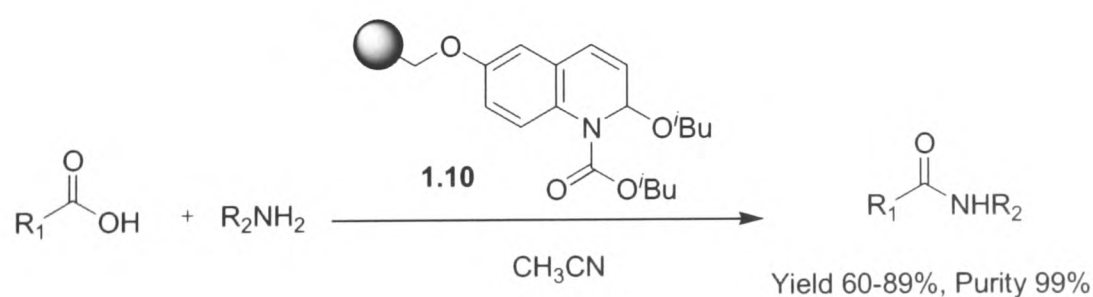


- **Coupling reactions:** amide bonds are present in a large number of pharmacologically active compounds, and a number of methods for their formation have been developed using polymer-supported reagents (Scheme 1.16). However, only few are commercially available, probably because amide bond formations are mainly used in peptide synthesis, which are usually carried out on solid phase, with the coupling reagent being in solution.



**Scheme 1. 16** Amide bond formation supported reagents

Carbodiimides like DCC<sup>64</sup> and EDC<sup>65, 66</sup> have been successfully immobilised. Once a carbodiimide is linked to a resin, the by-product urea derivative is retained on the solid phase and then is readily removed by filtration. These reagents have been also successfully applied to the synthesis of esters,<sup>67</sup> acylsulfonamides,<sup>68</sup> and amides.<sup>69</sup> Crosignani et al.<sup>70</sup> reported the development of a polymer-supported 2-chloro-N-pyridinium triflate (PS-Mukaiyama reagent) which appeared to work very efficiently for the synthesis of esters and amides including hindered substrates, secondary amines and anilines of 2,4,5-trisubstituted-2-oxazolines. Recently, the synthesis and application of polymer-supported 2-isobutoxy-1-isobutoxycarbonyl-1,2-dihydroquinoline (PS-IIDQ)<sup>71</sup> **1.10** as a coupling reagent has been reported (Scheme 1.17).



**Scheme 1. 17** Application of polymer-supported IIDQ in the synthesis of amides



PS-IIDQ was more efficient for general amide-bond formation than many classic agents [e.g. *N,N,N',N'*-tetramethyl-*O*-(7-azabenzotriazol-1-yl)-uronium-hexafluorophosphate (HATU), phosphoric acid bis (2-oxooxazolidide) chloride (BOP-Cl); and (Benzotriazol-1-yloxy)-tripyrrolidinophosphonium hexafluorophosphate (PyBOP)]. Moreover, after regeneration, the coupling efficiency was very similar to the fresh material.

#### 1.4. 2 Polymer-supported catalysts

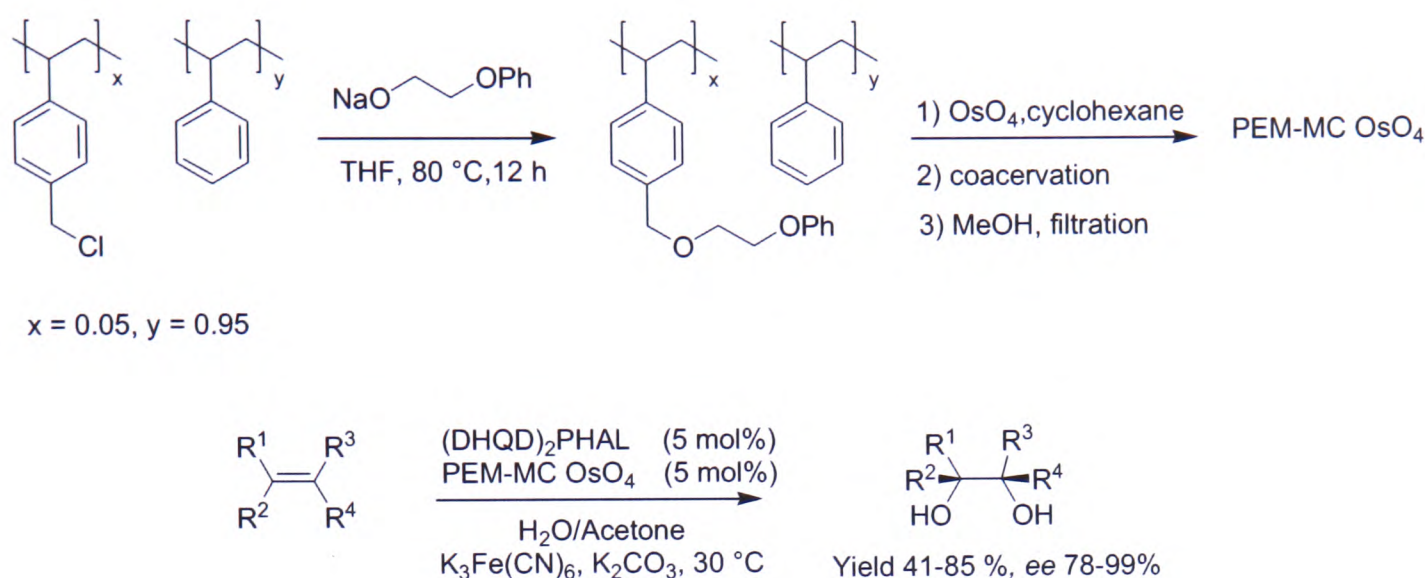
Chemical transformations often require a catalyst to increase the reactivity of one or more species involved; but the presence of a catalyst complicates work-up, making product purification and catalyst recycling difficult. Clearly functionalised polymers have found obvious applications in catalysis, in particular; polymer-bound catalysts with precious metal are especially beneficial in recovery and recycling for economical and environmentally friendly reasons (Scheme 1.18).



**Scheme 1. 18** General scheme of polymer-supported catalysts

For example, osmium-catalysed asymmetric dihydroxylation of olefins provides an efficient method for the preparation of chiral diols.<sup>72</sup> However, the high cost of osmium and ligands as well as the high toxicity of osmium catalysts, which may contaminate the obtained products, limit their use in industry. Over the past few years, much effort has been dedicated to developing solid-supported osmium-catalysts.<sup>73</sup> In 1998 a new approach was developed by Kobayashi; the so-called microencapsulation immobilisation of catalysts into polymers.<sup>74</sup> In this approach osmium tetroxide ( $\text{OsO}_4$ ) is physically enveloped by thin films of polystyrene, and at the same time immobilised by interaction between  $\pi$  electrons of the benzene rings of the polystyrene and vacant orbitals of the catalysts. The catalyst was successfully used in asymmetric dihydroxylation in water,<sup>75</sup> it was recovered quantitatively by

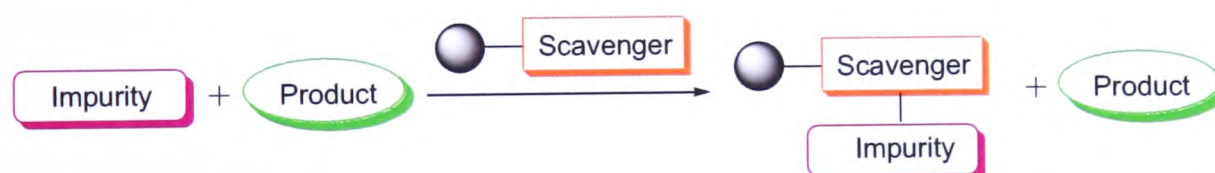
simple filtration and then re-used several times without loss of activity (Scheme 1.19).



**Scheme 1. 19** Synthesis of microencapsulated OsO<sub>4</sub> and its application in asymmetric dihydroxylation of olefins

### 1.4. 3 Polymer-supported scavengers

In the polymeric scavenger approach, by-products and excess reagents are selectively removed from solution via binding to an insoluble polymer (Scheme 1.20).<sup>76</sup>



**Scheme 1. 20** General scheme of polymer-supported scavengers

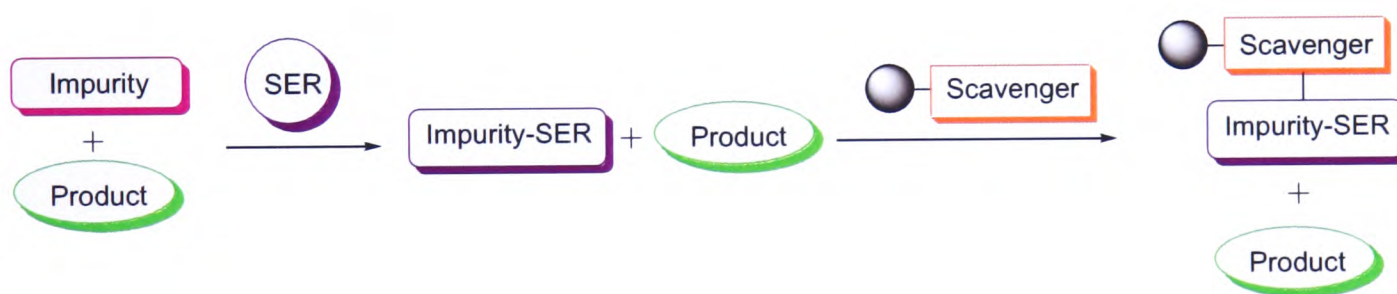
Polymer-supported scavengers can be divided roughly in two different classes: ionic scavengers (acidic or basic reagents) and covalent scavengers (nucleophilic or electrophilic reagents; Table 1.1).<sup>77, 78</sup>



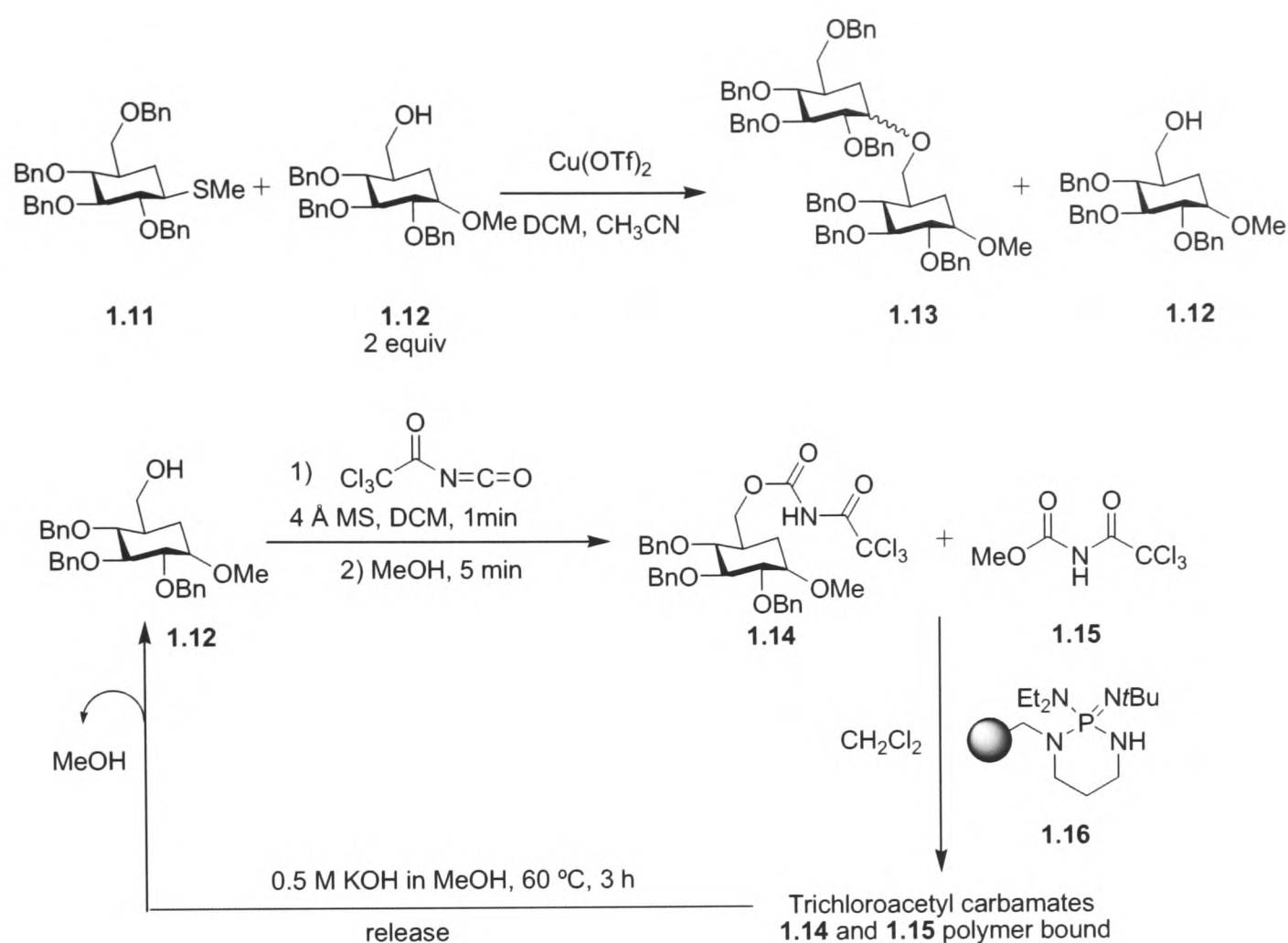
**Table 1. 1** Classes of polymeric scavengers

Acid	Base	Electrophilic	Nucleophilic

Sometimes the species involved in the chemical transformation are poorly reactive and direct sequestration is not possible. The addition of a sequestration enabling reagent, which is a highly reactive reagent, quantitatively transforms the poorly reactive impurity into a chemically activated species enabling therefore the easy trapping by a scavenger (Scheme 1.21).<sup>56</sup>

**Scheme 1. 21** General application of sequestering enabling reagent for purification

A recent example of this technique is represented by the use of trichloroacetyl isocyanate, as a sequestering enabling reagent of sugars, in the synthesis of oligosaccharides (Scheme 1.22).<sup>79</sup> Once the glycosidation of the compound **1.11** in the presence of an excess of **1.12** was completed, the reaction mixture was filtered and after an aqueous workup a mixture of anomers of the target disaccharides **1.13** and unreacted **1.12** was recovered. The sugar **1.12** was scavenged by trichloroacetyl isocyanate. The urethane **1.14** was obtained almost instantaneously under neutral conditions. Then, the reaction mixture was quenched with a large excess of MeOH that transformed unconverted trichloroacetyl isocyanate into methyl urethane **1.15**.

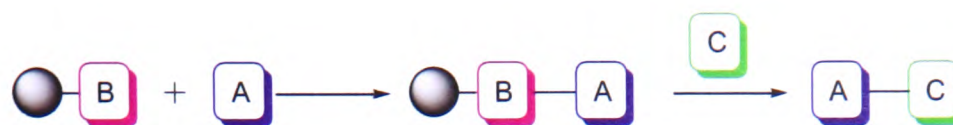


Scheme 1.22 Example of sequestration enabling reagent

Solid-phase sequestration of **1.14** and **1.15** was carried out using the highly basic, non-nucleophilic polymer-supported BEMP **1.16** to give ionic bound urethanes to the polymer.

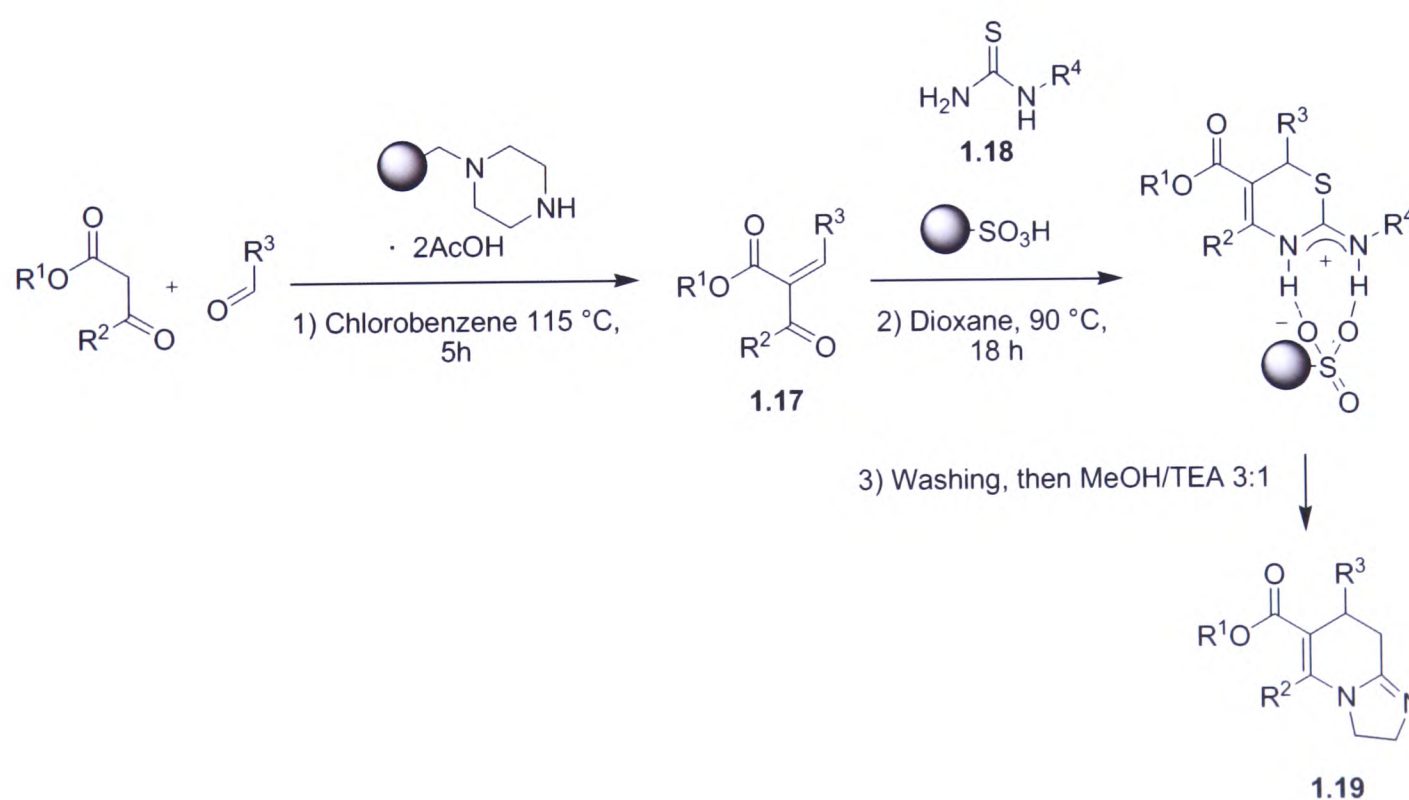
## 1.5 "Catch-and-release" methodology

The hybrid technique called "catch-and-release"<sup>80</sup> has been utilised over the years as a method to purify reaction products.<sup>81</sup> The target molecule of the reaction is selectively captured by a suitably functionalised polymer support either covalently or by an ionic bond. After filtration and washing, the product is released from the support using a particular reagent (Scheme 1.23).



**Scheme 1. 23** General scheme for "catch-and-release" methodology

Recently, few researchers have reported a new application of this technique where a functionalised polymeric supported reagent could be utilised not only to activate a specific chemical reaction but also act as a scavenger and selectively remove the desired product from the reaction mixture.<sup>82</sup> For example, in the synthesis of a library of 1,3-thiazines,<sup>83</sup> after the first step, which involved a Knoevenagel condensation of  $\beta$ -keto esters with aldehydes, enones **1.17** were treated with the appropriate thioureas **1.18** and polymer-bound sulfonic acid. The substrate was trapped on the polymer-bound sulfonic acid, which is the mediator of a ring-closure reaction and at the same time a scavenger of the desired product. Finally, after filtration 1, 3-thiazines **1.19** were cleaved from the resin by displacement with triethylamine. These releasing conditions generally proceeded in high yield and excellent purity without the need for further purification steps (Scheme 1.24).



**Scheme 1. 24** Application of "catch-and-release" strategy for 1, 3-thiazines synthesis

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## 1. 6 Conclusions

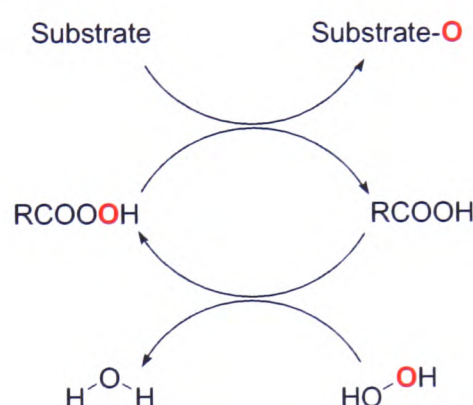
A wide range of polymer-supported reagents have been reported, but there is still space for expansion and development of new supported reagents, catalyst and scavengers. Polymer-assisted solution-phase synthesis has demonstrated its value as an important tool for high-throughput synthesis over the past few decades, with the simplification of work-up and automation being responsible for its success. Even if the cost of many supported reagents is not a strong point, this is counterbalanced by the efficacy of these tools which are becoming more and more used in the everyday laboratory research. Moreover, as the support optimisation is going on, these techniques are starting to be in use in scale up labs for the rapid synthesis and purification of active pharmaceutical ingredients and fine chemicals.



## 2. Synthesis of polymer-supported peracid

### 2.1 Introduction

Aqueous  $\text{H}_2\text{O}_2$  is an ideal, clean oxidant,<sup>84</sup> but the use, storage, and transportation of high concentrated peroxide (>60%) are not desirable for safety reasons. Although hydrogen peroxide is a potent oxidant, reaction rates are slow and typically need an activating agent to be used. Usually a mediator,<sup>85</sup> such as an organic or inorganic acid is used, which once converted to peroxyacid allows the organic substrate to be oxidised (Figure 2.1).



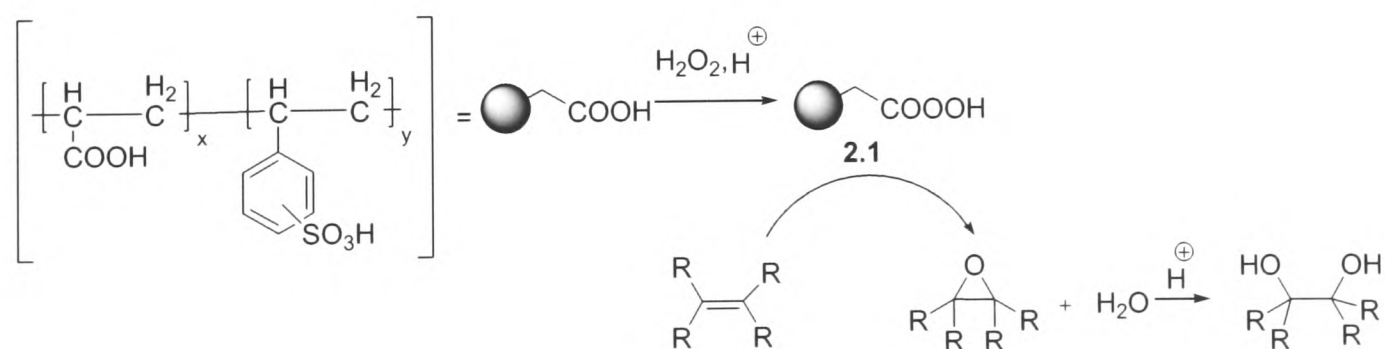
**Figure 2. 1** Oxidation of a substrate by  $\text{H}_2\text{O}_2$  in the presence of an activator

Peroxy-carboxylic acids are common oxidants in a wide range of chemical transformations, but their use is often banned due to associated handling risks.<sup>86</sup> Some relatively stable peracids, such as *meta*-chloroperoxybenzoic acid, are commercially available, but quenching of unreacted species followed by extraction and/or chromatography separation are often required. In addition, their use with chlorinated solvents represents a potential environmental hazard.<sup>87</sup> While, most of these reagents prove not to be satisfactory for medium- to large-scale synthesis, due to the high costs of formation and unfavourable by-products, supported carboxylic acids can be activated by hydrogen peroxide, avoid by-product formation and simplify the process of oxidation of the substrate. However, supported peroxy-carboxylic acids have been little studied and only a few examples have been reported in literature. The main drawback of these materials, which are typically

based on gel-type polystyrene,<sup>88-92</sup> acrylic polymers<sup>93</sup> and modified silica,<sup>94, 95</sup> is their poor loading level. These immobilised peroxy-carboxylic acids have been applied in the synthesis of epoxides<sup>96, 97</sup> from unsaturated hydrocarbons and the oxidation of sulfides.<sup>98</sup> Carboxylic ion-exchange resins with an acrylic macroporous matrix can be easily oxidised to give highly functionalised supported peroxy-carboxylic acids, but the high number and the proximity of strongly oxidative groups can make the handling of the dry supported reagents potentially unsafe (explosive).<sup>99</sup> The challenge to synthesise a safe and reliable supported reagent able to replace commercial peroxy-carboxylic acids in the laboratory practice is opened. In the following sections an overview of several previous attempts is discussed.

## 2. 2 Polymer-supported reagents containing peroxy-acids

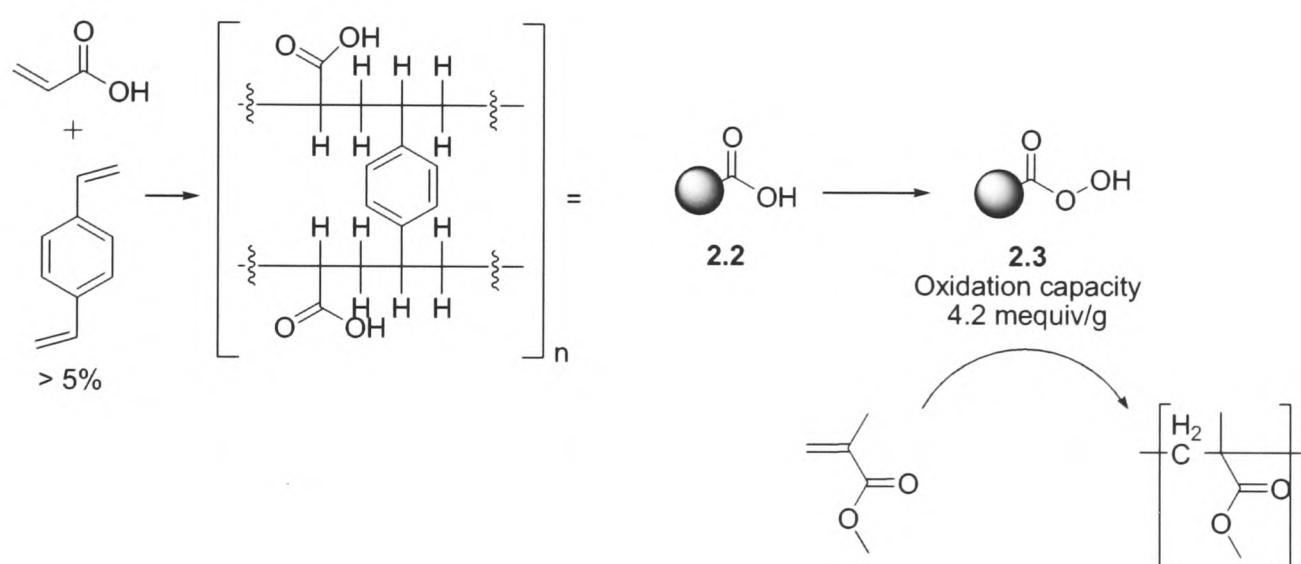
The first example of polymer supported peroxy-acids was reported by Helfferich,<sup>88</sup> a bifunctional cation exchange resin with carboxylic and sulfonic acid groups was oxidised with aqueous hydrogen peroxide, which converted carboxylic acid groups into percarboxylic acid groups. This peracid resin **2.1** was used to oxidise double bonds to give  $\alpha$ -glycols, but failed to give epoxide in good yields, probably due to the rapid opening of the epoxide ring under the strongly acidic conditions. In addition, these polymers were fragile, could only be used only for a few oxidative cycles and were restricted only to aqueous solvents (Scheme 2.1).



**Scheme 2. 1** Hydroxylation of olefinic double bonds by Helfferich's peroxy-acid resin **2.1**



Subsequently, Takagi<sup>100</sup> prepared peracid type resins, without sulfonic acid groups, by oxidation of carboxylic groups with *p*-toluenesulfonic or methanesulfonic acid and hydrogen peroxide. Good results were obtained when Amberlite XE-89 (cross linked polymethacrylic acid) was used. This peracid type resin showed an oxidation capacity or loading of 6.5 mequiv/g with a 62% of conversion of the carboxylic groups on the resin to percarboxylic acid groups. These peracid resins were used to oxidise olefins to epoxides in good yields. Koyama<sup>101</sup> found that the peracid resin could act as a radical initiator for vinyl monomers (e.g. polymerisation of methyl methacrylate). Peracid resins, **2.3** prepared by oxidation of the ion exchange resin Amberlite IRC-50<sup>®</sup> **2.2** with 60 wt. % aqueous hydrogen peroxide in the presence of *p*-toluenesulfonic acid at 45 °C for 16 hours, showed an oxidation capacity of 4.2 mequiv/g (Scheme 2.2).



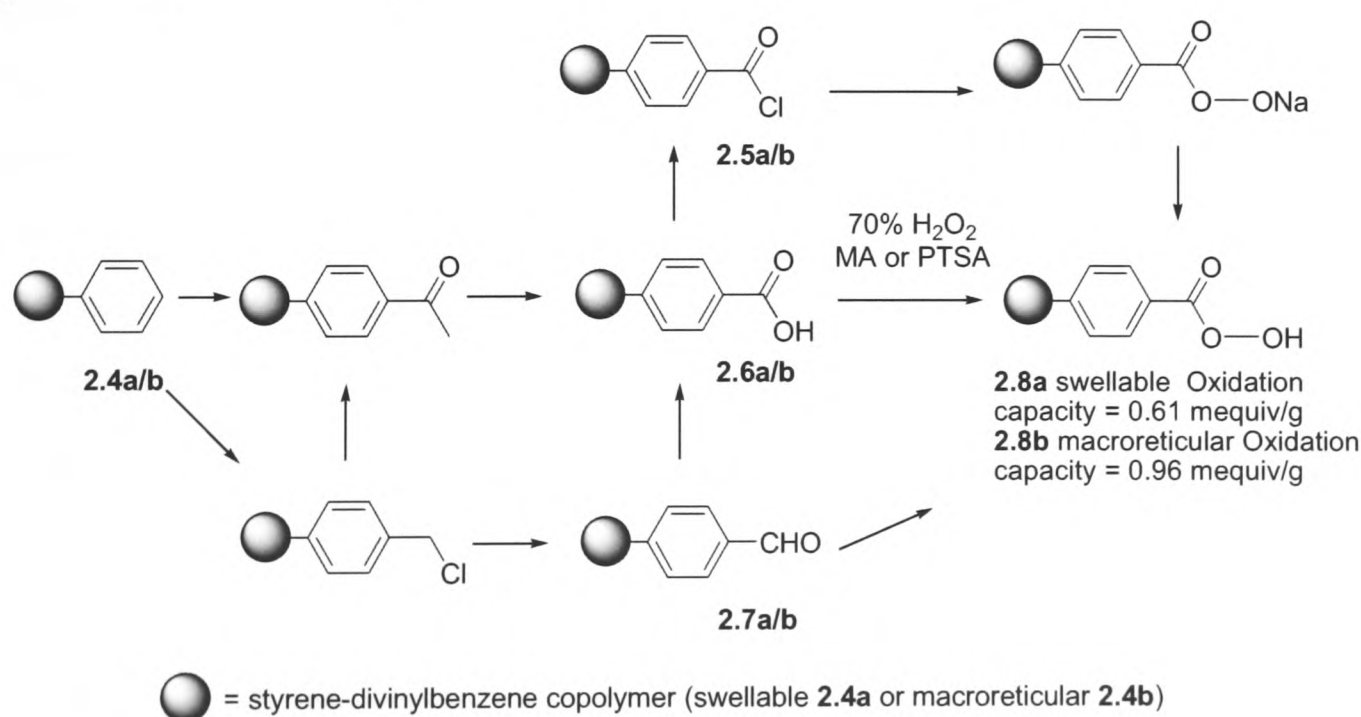
**Scheme 2. 2** Polymerisation of methyl methacrylate by peroxy-acid resin **2.3**

However Takagi<sup>99</sup> ascertained that Amberlite IRC-50<sup>®</sup> **2.2** could not be converted to a peracid type resin with an oxidation capacity greater than 1.3 mequiv/g in sulphuric and sulfonic acid media. In 1974, Takagi reported the synthesis of other peracid type resins prepared by the oxidation of Amberlite IRC-84<sup>®</sup> (polyacrylic acid, crosslinked to vary degrees of divinylbenzene), with hydrogen peroxide in sulphuric or sulfonic acid. These peracid resins showed high oxidation capacity (4.7-6.8 mequiv/g). It was recommended that the preparative conditions were chosen with care to ensure that

the oxidation capacity of the resin was below 7 mequiv/g as higher loading peracid resins are known to be explosive.<sup>100</sup> It was stated that the resins became yellowish whenever they were converted to the peracid form, while the deep yellow or brownish resins were generally dangerous. Moreover, the evaporation of the solvent and contact with a metal spatula had to be strictly avoided for a safe handling.

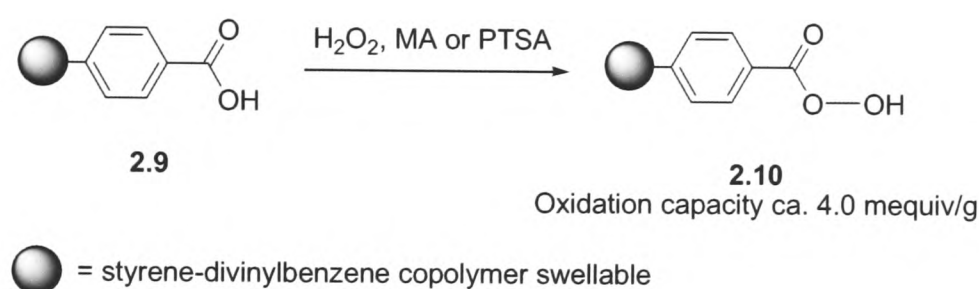
### 2.2. 1 The use of styrene-divinylbenzene copolymers as supports for peroxycarboxylic acids

In 1975, Fréchet and Haque<sup>89</sup> prepared insoluble polymers by chemical modification of styrene-divinylbenzene copolymers. One was a hydrophobic swellable copolymer containing 1 or 2 % divinylbenzene **2.4a** and the second was a rigid macroreticular resin **2.4b**. Three types of functionalised styrene-divinylbenzene copolymers (swellable **a** or macroreticular **b**) were used as precursors for the peracid resins, containing: vinylbenzoyl chloride units **2.5a/b**, vinylbenzoic acid units **2.6a/b** and vinylbenzaldehyde units **2.7a/b**. Peracid resin **2.8a** (containing co-polymers prepared on the 1 or 2 % crosslinked supports) could be only used after swelling of the polymer beads in solvents such as carbon tetrachloride, chloroform, dioxane or tetrahydrofuran. In contrast macroreticular peracid resin **2.8b** could be used in almost any solvent (Scheme 2.3).



**Scheme 2. 3** Oxidation of styrene-divinylbenzene resins **2.8a/b** by Fréchet's method

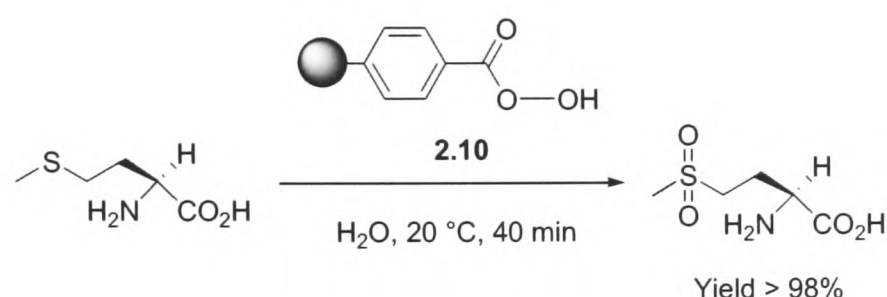
In all cases the peracid resins **2.8a/b** were found to be quite stable, they could be dried and stored in a refrigerator for long periods of time without appreciable loss of activity. The macroreticular peracid resin was found to be much more fragile and the portion of fine particles, due to beads degradation, increased with each oxidation-reduction cycle. The repeated stirring of the resin was found to be the cause for such breaking up of the large resin beads. In 1976, Hodge<sup>91</sup> prepared the similar resin **2.10**, containing aromatic peroxy-acid residues, by treatment of carboxy-substituted polystyrene resins **2.9** with 85% hydrogen peroxide in methanesulfonic acid (Scheme 2.4).



**Scheme 2. 4** Oxidation of carboxy functionalised styrene-divinylbenzene resin by Hodge's method

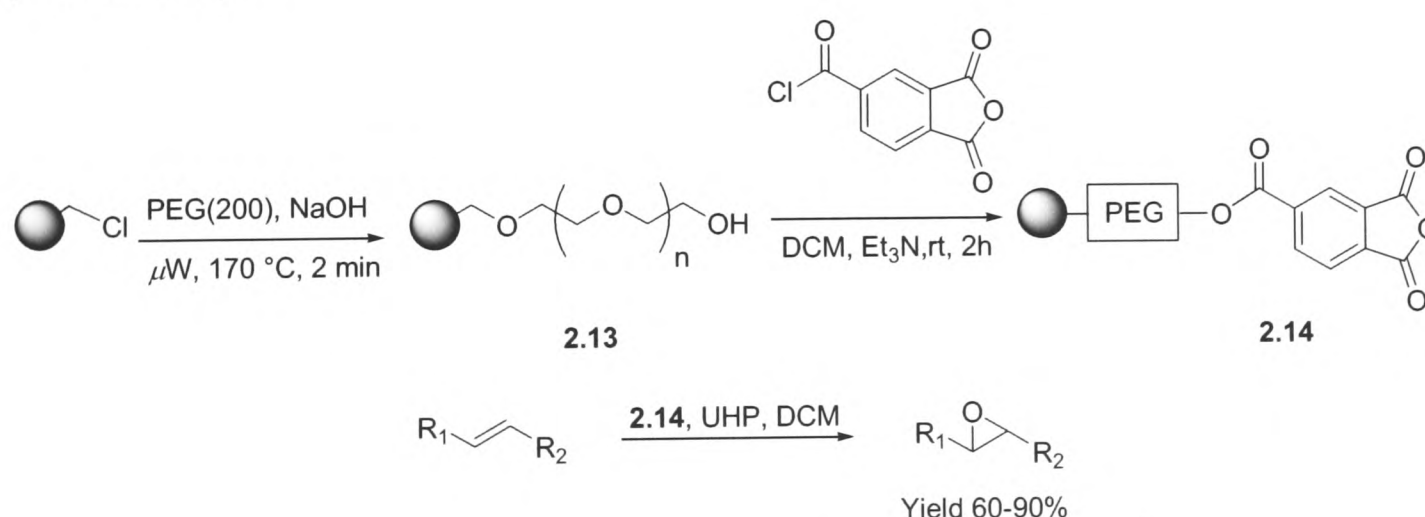
The oxidative capacities of this resin (3.5-4.0 mequiv/g) were 4 times greater than Fréchet's resins **2.8a** and comparable to commercially available 85% *meta*-chloroperbenzoic acid (5 mmol/g). The carboxy-resin **2.10** showed that 80% of the phenyl residues were substituted, where in Fréchet's resin **2.8a** only 15% were converted. This may result in substantial differences in the swelling properties of the resins and hence in the availability of reactive groups in different solvents. Hodge's resins **2.10** reacted with many di- and tri-substituted olefins to give epoxides in good yield, but using monosubstituted olefins the yield was poor. This is not surprising, as the peroxy-acid resin used in THF would be expected to be less reactive than both *meta*-chloroperoxybenzoic and perbenzoic acid which were used in chloroform as a solvent.<sup>102</sup> Hodge also used peracid resin **2.10** to oxidise sulfides, mainly penicillins and deacetoxycephalosporins, to sulfoxides or sulfones.<sup>98</sup> Moreover, the separation of the polymer-supported peracid from the already acidic reaction mixtures was quite advantageous.

Many of these oxidations proceeded in high yield and in several cases the removal of the polymer-supported reagent gave a solution containing only the desired sulfoxide or sulfone (Scheme 2.5).



**Scheme 2. 5** Oxidation of *L*-methionine by Hodge's peracid resin **2.10**

Recently Taddei has reported the epoxidation of a series of alkenes using a supported peracid generated *in situ* by the oxidation of a novel PS–DVB supported phthalic anhydride using an urea–hydrogen peroxide complex.<sup>90</sup> Merrifield resin was submitted to "PEGylation"<sup>103</sup> using PEG with a molecular weight of 200, under microwave irradiation, to give **2.13**. Subsequently resin **2.13** was treated with trimellitic anhydride chloride in DCM and triethylamine to give supported anhydride **2.14**. The reaction of a variety of alkenes with resin **2.14** in the presence of a urea–hydrogen peroxide adduct gave complete conversion to the corresponding oxirane (Scheme 2.6).

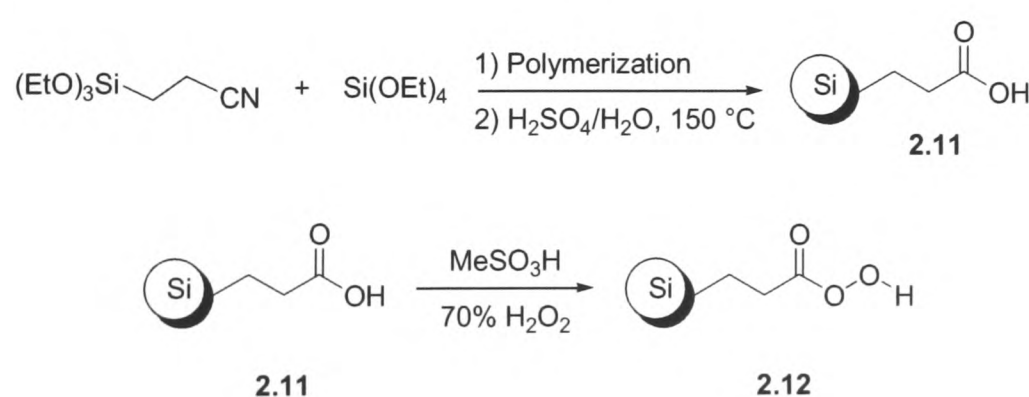


**Scheme 2. 6** Alkene epoxidation with UHP complex and PS–DVB supported phthalic anhydride



### 2.2.2 The use of inorganic oxides as supports for peroxycarboxylic acid

Sherrington reported the synthesis and the use of polystyrene resins, with nominal crosslinking ratios of 5–40%, and various commercially available silicas and aluminas as a support for the oxidation of tetrahydrothiophene.<sup>92</sup> A difficulty to functionalise the resins was observed with the increase of the crosslinking level, although resistance to oxidative degradation by hydrogen peroxide in methanesulfonic acid was enhanced. Two different linkages were employed for the attachment of peroxy-acid groups to the inorganic oxide supports, one involving a direct silicon aromatic bond and the other via an ethylene bridge. In both cases, the introduction of peroxy-acid groups proceeded easily and without any apparent degradation, although the loadings achieved were somewhat lower than expected. All supported peracid resins with a 5% level of crosslinking were shown to be highly effective. One macroreticular resin displayed partial selectivity in oxidising a thioether to sulfoxide rather than sulfone. The best of the inorganic oxide supported oxidants approached closely the reactivity shown by the 5% crosslinked resin. A mixed silica/alumina support showed the highest selectivity for sulfoxide formation when the peroxy-acid was attached by a direct silicon aromatic bond. The use of inorganic oxides as a support for peroxycarboxylic acid was also reported by Clark.<sup>94</sup> A hexagonal mesoporous silica was used as a support: tetraethyl orthosilicate and 2-cyanoethyltriethoxysilane were stirred at room temperature in a solution of water, ethanol and *n*-dodecylamine. The CN-silica obtained was hydrolysed by an aqueous solution of sulphuric acid to obtain a COOH-silica **2.11** that was afterwards oxidised to the corresponding COOOH-silica **2.12** (Scheme 2.7).

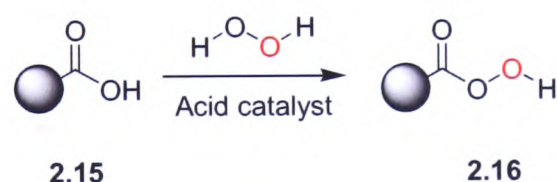


**Scheme 2. 7** Preparation of supported peroxycarboxylic acids **2.12** using templated sol-gel techniques

The material was also used in the oxidation of alkenes and ketones (Baeyer-Villiger).<sup>95</sup>

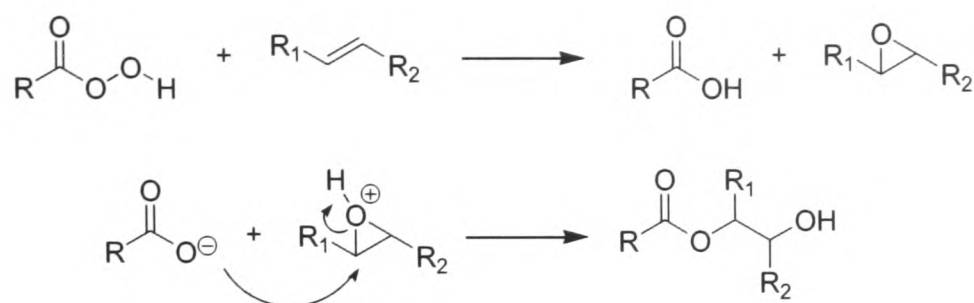
### 2.3 Project aims

The main aim of this PhD project was to prepare a polymer-supported peroxycarboxylic acid **2.16**, based on a commercially available weak-acid ion-exchange resin **2.15**. It was proposed that a supported reagent such as **2.16** would allow oxidation of a wide range of molecules avoiding tedious work-up associated with the use of peracids in solution phase. As the synthesis and the polymerisation of monomers demands a profound knowledge of polymerisation techniques and requires a lot of optimisation, the idea of functionalising a commercial ion-exchange resin offers advantages in terms of time and cost. For these reasons studies focused on the development of an easy and consistent synthesis to obtain a safe and reliable reagent, starting from inexpensive commercially available starting materials, were carried out (Scheme 2.8).



**Scheme 2.8** Oxidation of a carboxylic resin

Polymer-supported reagent **2.16** would be used to obtain complete oxidation of several substrates; isolation of the final product would be achieved simply by filtration of the polymer beads and solvent evaporation. In addition, one of the aims was to avoid the presence of side reactions, for example the formation of hydroxyl-esters in the epoxidation of alkenes (the carboxylic acid, generated from the spent peroxyacid, could react with the epoxide to form the ester, Scheme 2.9).



**Scheme 2. 9** Possible by-product formation in the epoxidation of alkenes by peracids

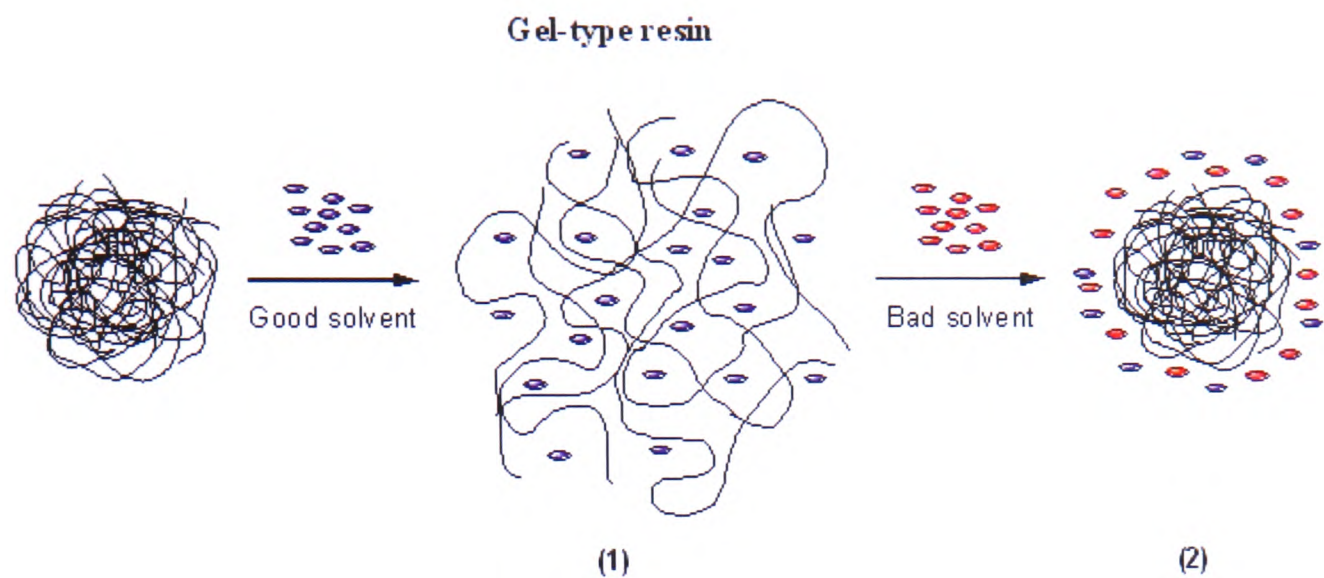
Using a supported reagent would allow an easy work-up and avoided liquid-liquid extractions or quenching of unreacted reagents, which would reduce the occurring of side reactions. Once prepared, the generality and scope of the polymer-supported peracid **2.16** would be explored in the oxidation of various substrates. This would involve, in particular, investigations of oxidations of sulfides, alkenes, pyridine derivatives and ketones.

## 2. 4 Results and discussion

### 2.4. 1 Characteristics of a macroporous type resin

Macroporous resins are prepared by carrying out the synthesis of the materials in the presence of an inert agent, which provides to template the matrix and is subsequently leached out, leaving pores or "macropores", that are considerably larger than those of the gel-type resins.<sup>104</sup> The IUPAC definition for "macroporous" resins refers to materials that have pores with a diameter greater or equal to 500 Å, the term has been generalised to resins that show a porous structure in the dry state.<sup>105</sup> On the other hand, for conventional gel-type resins, the molecular porosity is a result of the swelling process due to the interactions between the polymer and the solvent. An organic solvent may sorb into the polymeric structure and allows backbone rotation to occur. Such solvents are defined as thermodynamically good or swelling solvents. When a solvent interact poorly with a polymer is defined thermodynamically "bad", non-solvent, or precipitants. If a polymer is swollen in a "good" solvent, and an excess of a "bad" solvent is added, then the "pore structure" collapses and the polymer shrinks (Figure 2.2).





**Figure 2. 2** Solvent response of a gel-type resin: swelling in a good solvent (1); contraction of swollen gel after addition of a bad solvent (2)

However, the definitions of "macroporous" has been extensively debated. Millar,<sup>106</sup> who is a pioneer in the preparation of macroporous resin, defines macroporosity (in the case of crosslinked styrene-divinylbenzene resins) as the "uptake" from the dry polymer of 0.1 m<sup>2</sup> g<sup>-1</sup> of *n*-heptane (bad solvent) in 16 h. A more general definition for macroporous copolymers refers to materials prepared in the presence of a pore-forming agent (called porogen or diluent) and having a porosity in the dry state. In the past years different porogens have been used to prepare macroporous resins<sup>107</sup> and they can be divided in three main classes characterised by the pores size they can promote (Table 2.1).

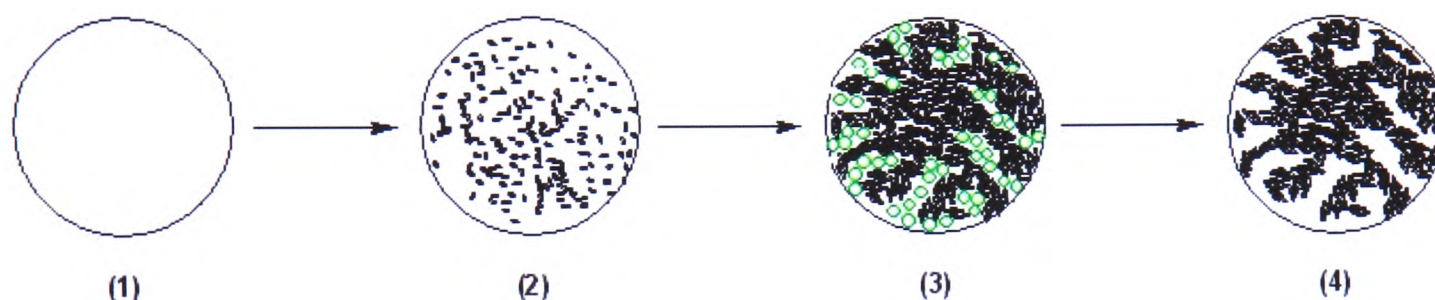
**Table 2. 1** General classification of diluents used in the preparation of macroporous resins

Type of porogen	Pore size Å	IUPAC definition	Examples of porogen
Solvating	<20 (small)	Micropores	toluene
Non-solvating	20-500 (large)	Mesopores	<i>n</i> -heptane
Polymeric	>500 (very large)	Macropores	linear polystyrene

The choice of porogen and its proportion, associated with the level of crosslinker can control the morphology of the final material. The effect of the diluent on pore



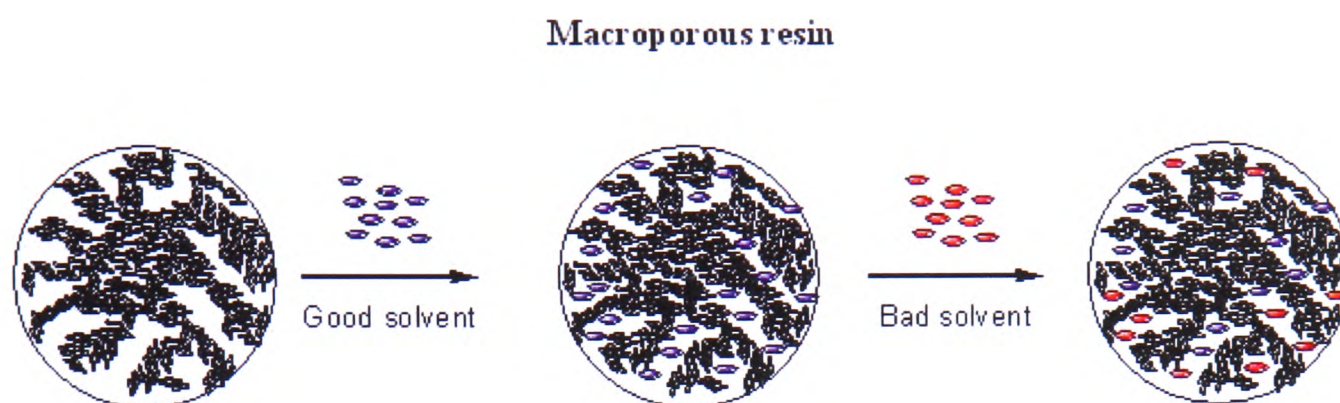
formation has been explained by Kunin<sup>108</sup> and Sherrington.<sup>109</sup> When polymerisation begins, spherical droplets are formed by the suspension/agitation process, and the monomers start to react to form the polymer matrix, this is in a highly solvated state, the particles formed into the droplets are often referred to as microgel. If the droplets contain a good solvent for the monomers, such as toluene, the particles are fully solvated until there is a high conversion to polymer. Thus when phase separation takes place (the polymer is no longer soluble in the solvent), the environment within the joined particle contains only a small amount of unreacted monomers, and the particles retain their identity with a network of pores (Figure 2.3).



**Figure 2. 3** Action of porogen in the preparation of a macroporous resin: (1) monomer, crosslinker and porogen isotropic solution; (2) polymer network forming; (3) porogen acts as pore template; (4) porogen removed to leave a "pore structure"

When a non-solvating porogen, such as *n*-heptane, is used, the microgel particles are poorly swollen and phase separation takes place early (low conversion to polymer). In this case, the droplet contains a high level of unreacted monomers and these have the effect not only of fusing the microgel particles together, but also of causing small pores. To improve the benefits of solid-supported reagents and scavengers, macroporous beads need to have a large surface area and large pores. While a high surface area provides more sites for functionalisation, large pores provide efficient transport of reagents through the bead. However, if a resin bead has a large surface area and a large number of pores, then each pore is likely to have a small diameter and vice versa. The rigid structure of a macroporous polystyrene matrix with fixed pores size (high DVB levels) gives to these resins a limited swelling in a wide range of solvents (even the good ones). This peculiarity can be used in organic synthesis

and in solid phase "macroporous resin assisted chemistry", without modification of the reaction conditions as required for gel-type resins (Figure 2.4).



**Figure 2. 4** Solvent response of a macroporous resin showing a limited swelling in good or bad solvents

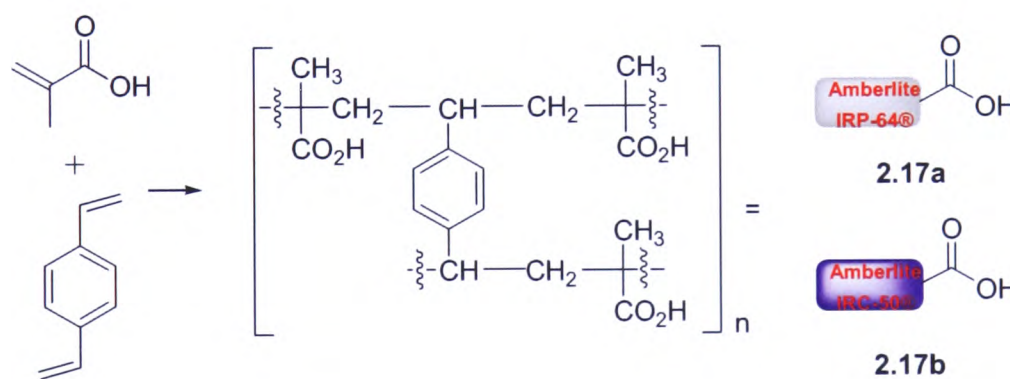
Moreover, the rigid structure makes these supports very robust towards mechanical agitation and ease to handle (macroporous resins do not stick like gel-type resins). A comparison between macroporous and 2% gel-based Merrifield resins was carried out by Janda,<sup>110</sup> who demonstrated how the washing of a dye from pre-treated resins was more efficient with a macroporous resin than a gel-type one. Comparison of a palladium catalyst, for Wacker olefins oxidation, supported on gel-type and macroporous resins gave better results on the macroporous support. Nowadays, it is possible to find a wide range of commercial macroporous resins exhibiting better efficiency and kinetics than gel-type resins in high polar solvents.

#### **2.4. 2 Synthesis of a novel peracid resin**

The commercially available weak-acid ion-exchange resins of interest described herein were based on a macroporous polyacrylic/polymethacrylic-divinylbenzene copolymer and contained a large number of carboxylic acid groups suitable for the desired oxidation. Because of the harsh reaction conditions, that involves the use of strong acids and hydrogen peroxide, our attention was focused on macroporous resins, which offer good chemical and physical stability. Moreover the rigid structure makes these supports compatible with a wide range of solvents; in fact their



reactivity is not limited by the swelling capacity. Three cation-exchange resins were evaluated for the preparation of polymer supported peracid: Amberlite IRC-50<sup>®</sup>, Amberlite IRP-64<sup>®</sup> and Dowex MAC-3<sup>®</sup>. These resins were chosen not only for their chemical and physical characteristics, but also due to their low cost (price, availability and scalability). Amberlite IRC-50<sup>®</sup> is the first example of macroporous resin made by the copolymerisation of methacrylic acid and divinylbenzene (Figure 2.5), it was commercialised by Rohm and Haas in 1948 and found an application in the preparation of high molecular weight antibiotics such as streptomycin.<sup>111</sup> Although Amberlite IRC-50<sup>®</sup> showed the typical characteristic of macroporous resin such as opaque appearance and high resistance to osmotic shock, it was not recognised for many years of being macroporous. Only twenty years later, Kun and Kunin<sup>112</sup> showed that Amberlite IRC-50<sup>®</sup> had relatively low, but significant, internal surface area and comparatively large pore size. Electron microscopy images confirmed a sponge-like structure typical of a macroporous resin with a low degree of porosity.



**Figure 2. 5** Structure of macroporous DVB-methacrylic acid resin **2.17a** and **2.17b**

Currently Amberlite IRC-50<sup>®</sup> has found a wide use in a variety of applications such as the neutralisation of strong bases; the recovery of metal ions, the isolation and concentration of basic amino acids, enzymes and peptides. Amberlite IRP-64<sup>®</sup> is an insoluble, weakly acidic cation-exchange resin (Figure 2.5), it is suitable especially as a carrier for certain basic (cationic) drugs and related substances. Amberlite IRP-64<sup>®</sup> resin is capable of binding different medicinal agents onto its insoluble polymeric matrix to overcome problems of taste in oral dosage formulations. Dowex MAC-3<sup>®</sup> resin is a high capacity, macroporous weak acid cation exchange resin

based on a polyacrylic-divinylbenzene matrix containing carboxylic acid functional groups (Figure 2.6), its physical stability give good resistance to osmotic shock. Generally, Dowex MAC-3<sup>®</sup> resin has been used for water treatment, but in the recent years has also found applications for the purification of antibiotics, drugs and amino acids.

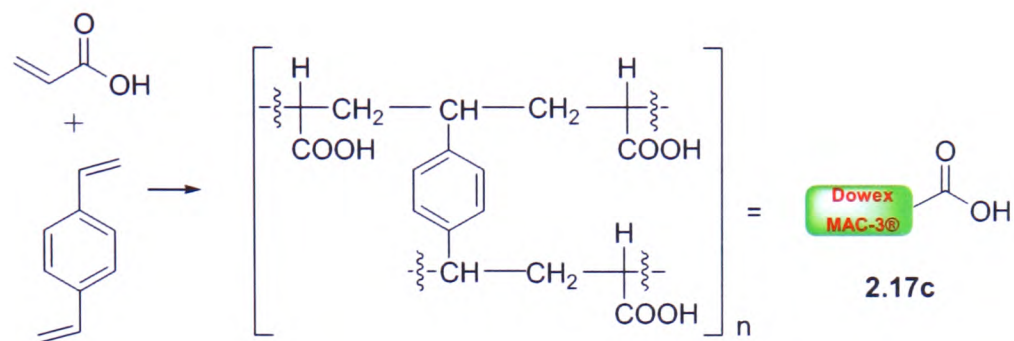


Figure 2. 6 Structure of macroporous DVB-acrylic acid resin 2.17c

Table 2.2 summarised the main physico-chemical characteristics of the three resins 2.17a-c provided by the resin manufacturers.

Table 2. 2 Ion exchange resins

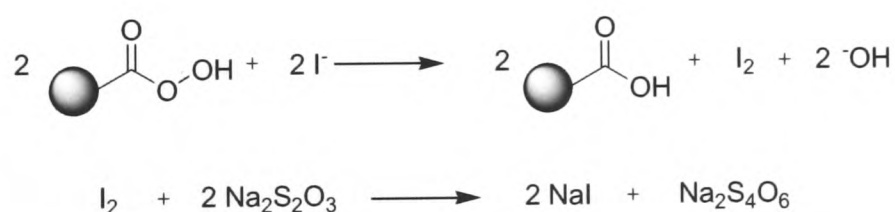
Ion-exchange resin	Amberlite IRP-64 <sup>®</sup> 2.17a	Amberlite IRC-50 <sup>®</sup> 2.17b	Dowex MAC-3 <sup>®</sup> 2.17c
Bead size	38-150 µm	300-1180 µm	300-1400 µm
Average pore size	800 Å	<100 Å	>500 Å
Surface area	n.a	2.2 m <sup>2</sup> g <sup>-1</sup>	n.a.
Particle density	1.50 g/mL	1.10 g/mL	1.18 g/mL
Monomers	Methacrylic acid-DVB	Methacrylic acid-DVB	Acrylic acid-DVB
Matrix	Macroporous	Mesoporous	Macroporous
Ionic form	H <sup>+</sup>	H <sup>+</sup>	H <sup>+</sup>
pK <sub>a</sub>	4.0	5.5	5.0
Water content	10 %	66 %	50 %
Total exchange capacity	3.5 equiv/L 10.0 equiv/g	3.8 equiv/L 10.4 equiv/g	4.0 equiv/L 10.0 equiv/g
Physical form	White opaque beads	White opaque beads	White opaque beads
Max. operating T	<120°C	<100°C	<120°C
Manufacturer	Rohm and Haas	Rohm and Haas	Dow Chemical
Price	140£/Kg	200 £/Kg	60 £/Kg

The clear difference among the acrylic resins is the particle size, which vary from a maximum of 150  $\mu\text{m}$  for Amberlite IRP-64<sup>®</sup> to 1180  $\mu\text{m}$  for Amberlite IRC-50<sup>®</sup>. Dowex MAC-3<sup>®</sup> differs from the Amberlite resins because of its monomers composition (acrylic acid-DVB) and has bigger particle size (1400  $\mu\text{m}$ ). A comparison of the  $\text{pK}_a$  values indicates that the methacrylic acid resin (Amberlite IRC-50<sup>®</sup>) has a weaker acidity than the other ones, all three present comparable value of exchange capacity. Another difference among these materials is the porosity, which ranges from 100 Å (Amberlite IRC-50<sup>®</sup>) to 800 Å (Amberlite IRP-64<sup>®</sup>). As these resins coming from the supplier had a certain content of water and contaminants, it was necessary to perform several washing and regenerating cycles. Therefore, prior to their use the beads were washed in a soxhlet with methanol for 48 h and centrifuged to remove the adherent liquid, rapidly washed with methanol and dried at 40 °C in a vacuum oven. The conditioning procedure was carried out in the following manner: the beads were washed for 10 times alternating 1 M NaOH, deionised water and 1 M HCl. The resins were stored in 0.1 M HCl overnight, washed with deionised water, methanol and finally dried at 40 °C in a vacuum oven. The oxidation of the carboxylic acid groups of the resins was accomplished by reaction with hydrogen peroxide at different concentrations in the presence of sulfuric acid or a sulfonic acid at different temperatures over various times. It was decided to use two different solutions of hydrogen peroxide: 30 wt. % and 50 wt. %. For the acid catalyst, it was decided to use: sulfuric acid, *p*-toluenesulfonic acid (PTSA) and methanesulfonic acid (MA). Moreover, various quantities of acid were investigated: 1, 2 and 4 equiv based on the loading of the resins. The mixture of the resin with the acid was gently stirred for 10 min, and then the peroxide was added dropwise at room temperature. The experiments were carried out at two different temperatures (30 °C and 50 °C) and for different times: 6, 16 hours. The resins were filtered and washed with methanol, until the washing solutions were free of hydrogen peroxide. The absence of hydrogen peroxide adsorbed on the resin was determined by cerium sulphate and a ferroin indicator (Scheme 2.10),<sup>113</sup> which is not sensitive for percarboxylic acid groups.



**Scheme 2. 10** Oxidation of  $\text{H}_2\text{O}_2$  by ceric sulphate

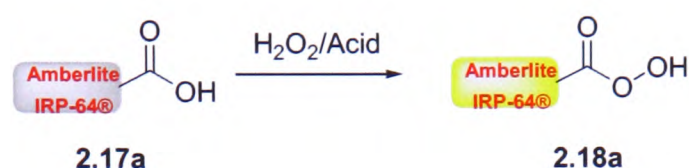
An aliquot of the oxidised resin was added to an aqueous solution of cerium sulphate and  $\text{H}_2\text{SO}_4$ . The mixture was stirred for 10 min at 30 °C. A colour change of the solution from orange-pink to light blue indicates the presence of hydrogen peroxide, in this case the resin requires further washing. The resin was subsequently dried under reduced pressure in the dark at room temperature for 16 hours. The oxidation capacity was determined by iodometric titration, which involved reacting a sample of the peracid resin in a solution of glacial acetic acid containing potassium iodide (1.1 equiv compared to the maximum theoretical loading), for 30 min at 40 °C. The suspension was then titrated with a volumetric standard solution of potassium thiosulfate (0.1 N) and starch indicator (one mole of peracid stoichiometrically liberates one mole of iodine; Scheme 2.11).<sup>114</sup> The diffusion of KI, the acid catalyst into the matrix and the visual error of the operator to determine the change of colour during the titration restricts the accuracy of the measurement of oxidation capacity, with an error of about  $\pm 10\%$ . In order to obtain a more accurate value, the titrations were repeated three times and corrections calculated from blank determinations with the respective unoxidised resins.

**Scheme 2. 11** Determination of the loading of the peracid resin by iodometric titration

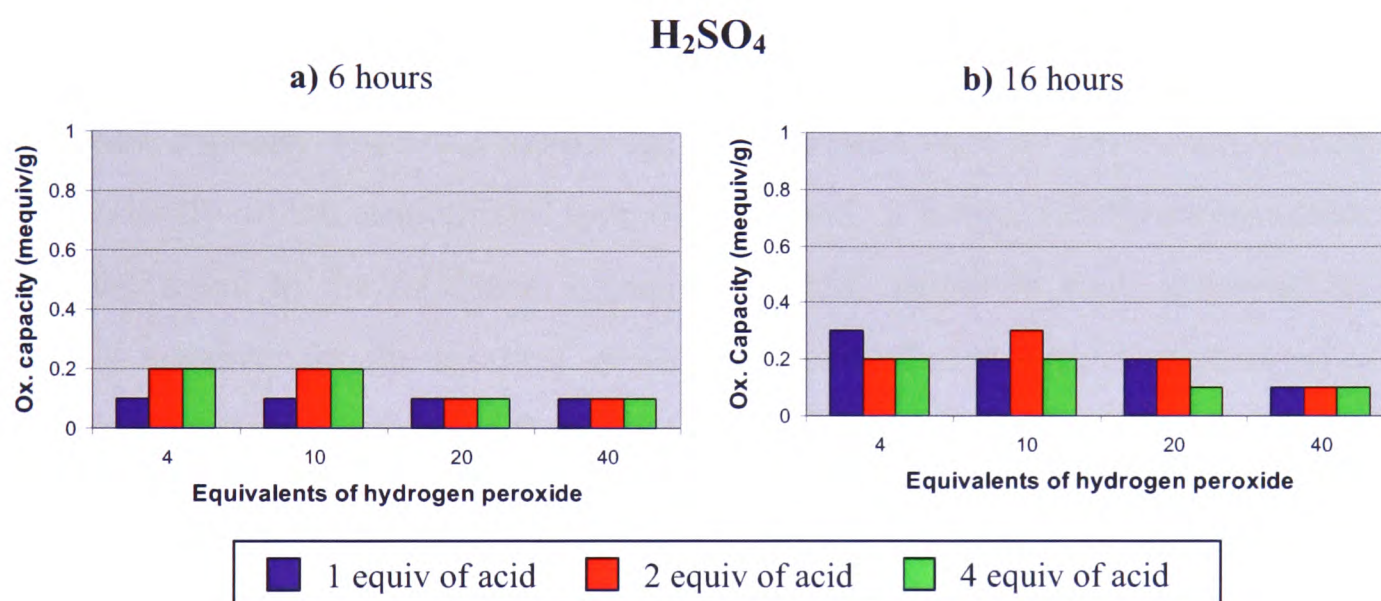
The oxidation of the resins will be discussed separately to facilitate the treatment of the data.

### 2.4. 3 Oxidation of Amberlite IRP-64<sup>®</sup>

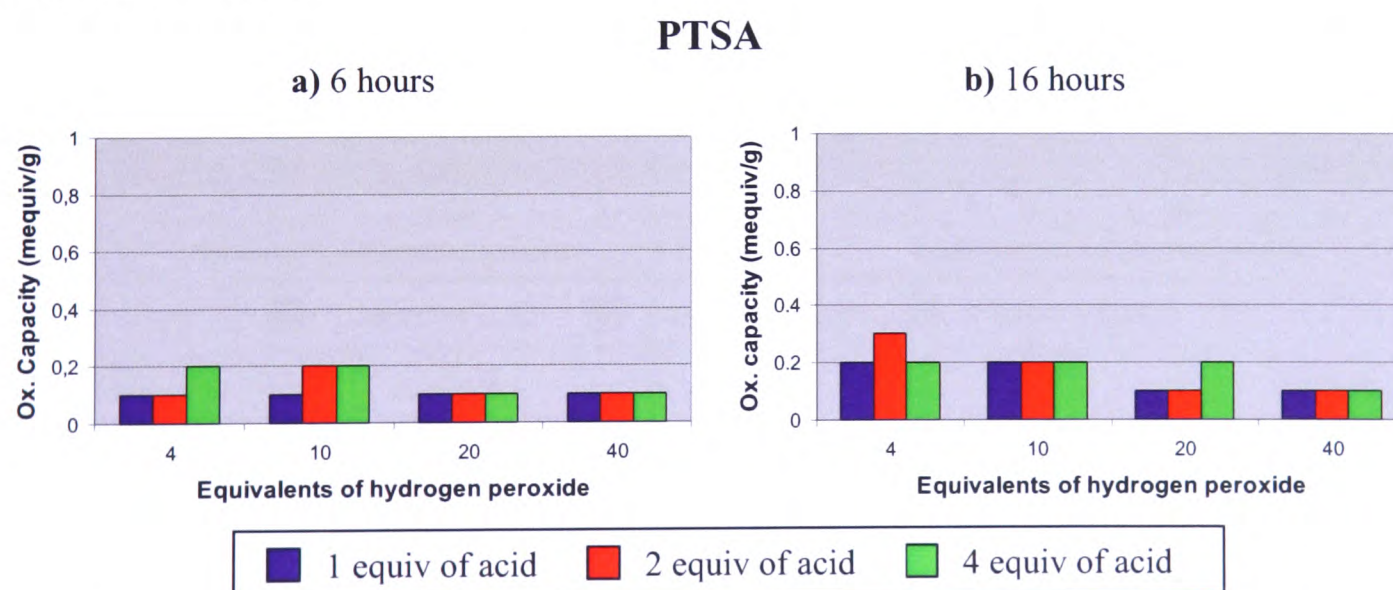
In the first screening, sulfuric acid and 30 wt. % hydrogen peroxide were used (Graph 2.1). All the experiments were carried out at 30 °C for 6 and 16 hours (Scheme 2.12). The same series of experiments were repeated with *p*-toluenesulfonic (Graph 2.2) and methanesulfonic acid (Graph 2.3).



**Scheme 2. 12** Oxidation of carboxylic resin Amberlite IRP-64<sup>®</sup> **2.17a**

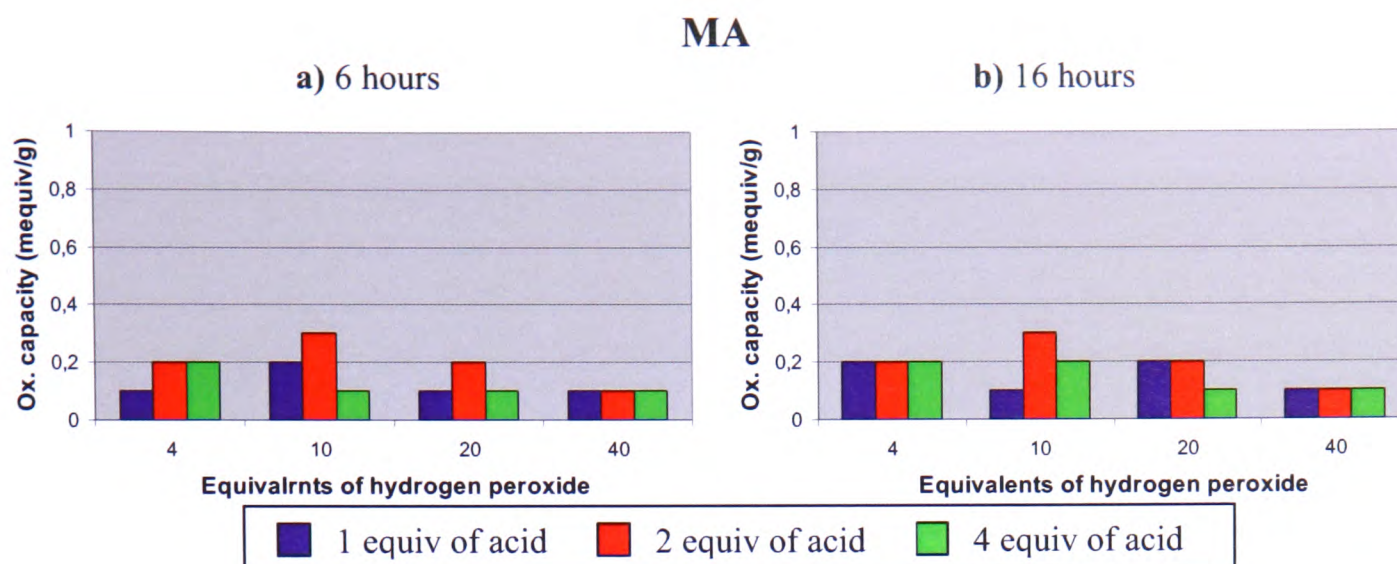


**Graph 2. 1** Activity of the peracid resins generated by Amberlite IRP-64<sup>®</sup> **2.17a** using H<sub>2</sub>SO<sub>4</sub> and H<sub>2</sub>O<sub>2</sub> 30 wt. % at 30 °C



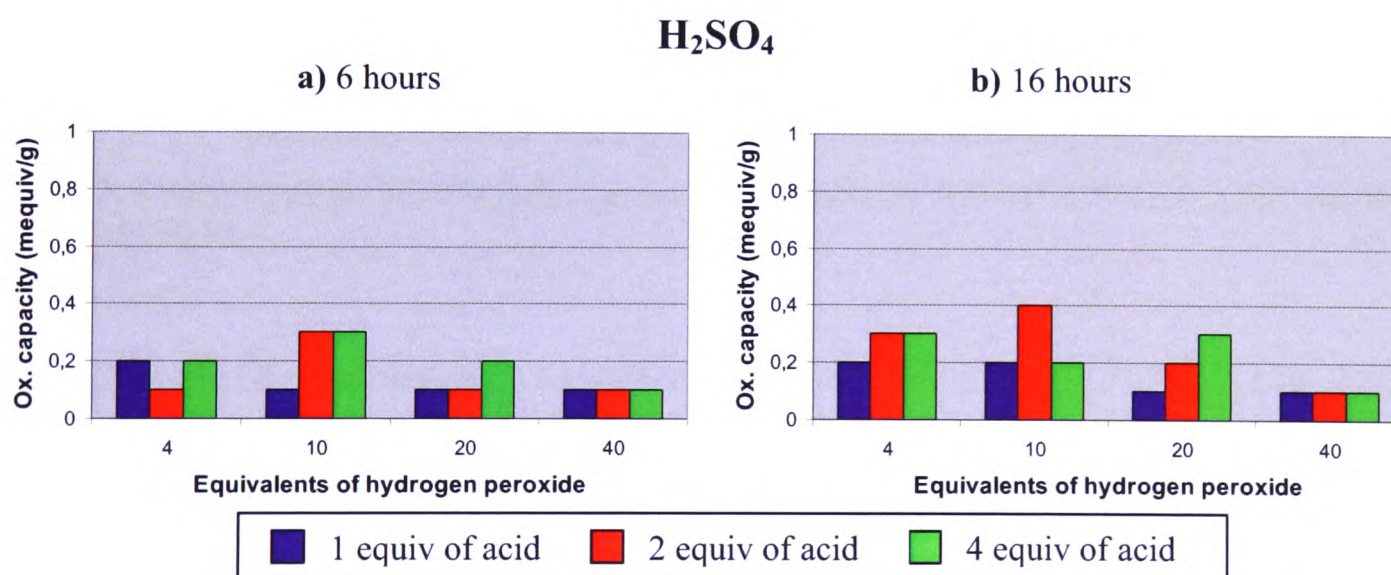
**Graph 2. 2** Activity of the peracid resins generated by Amberlite IRP-64<sup>®</sup> **2.17a** using PTSA and H<sub>2</sub>O<sub>2</sub> 30 wt. % at 30 °C



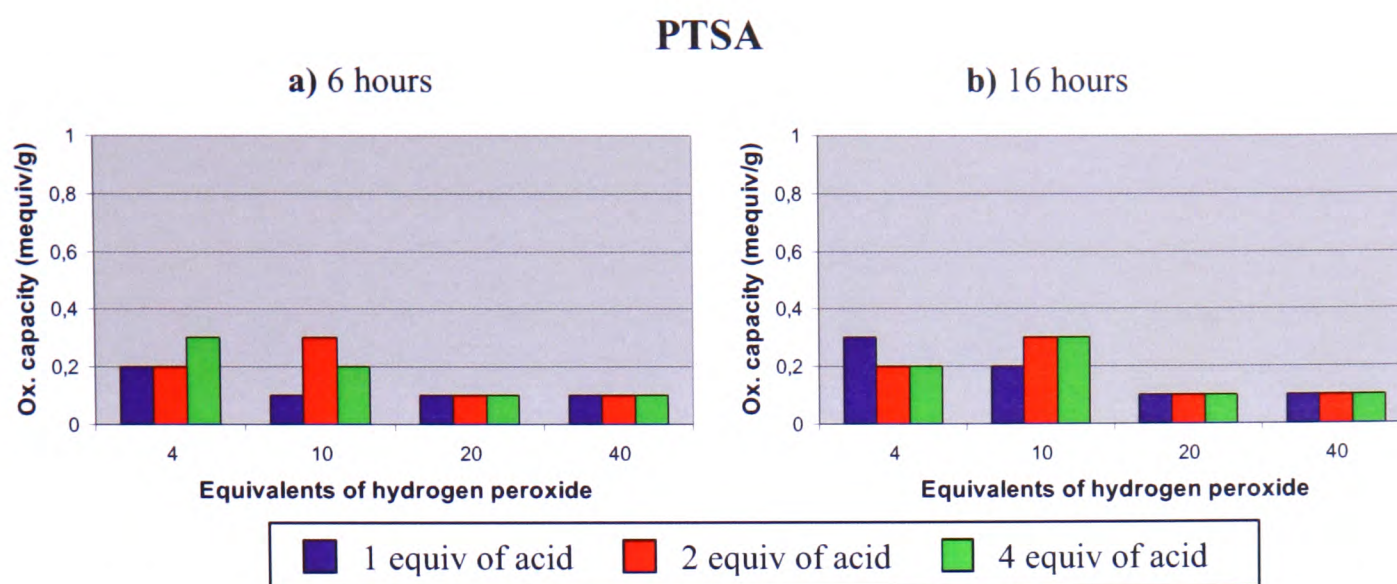


**Graph 2. 3** Activity of the peracid resins generated by Amberlite IRP-64<sup>®</sup> **2.17a** using MA and H<sub>2</sub>O<sub>2</sub> 30 wt. % at 30 °C

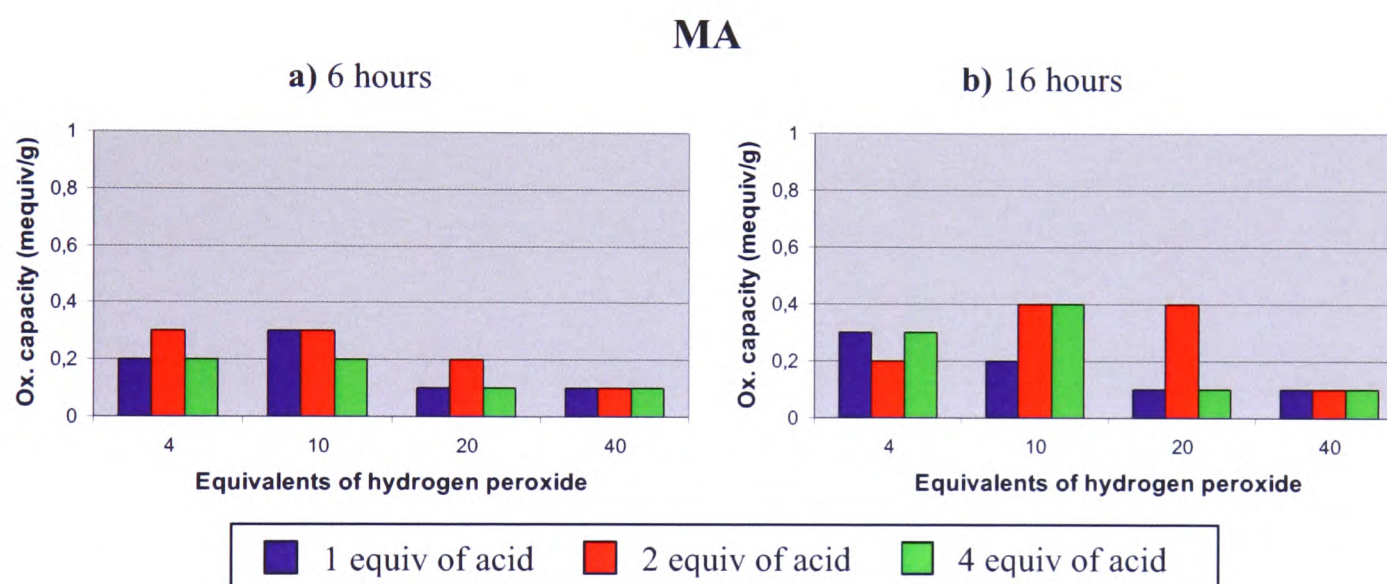
Amberlite IRP-64<sup>®</sup> **2.17a** showed little oxidation of carboxylic acid groups (oxidation capacity = 0.1-0.3 mequiv/g) when treated with 30 wt. % H<sub>2</sub>O<sub>2</sub> at 30 °C independently on the amount and type of acid used. A longer reaction time showed a little difference in the oxidation capacity, in fact variations were observed in the range of the error for the titration. A second series of experiments, performed at 50 °C, also showed low oxidation capacity (< 0.5 mequiv/g Graph 2.4, 2.5, 2.6).



**Graph 2. 4** Activity of the peracid resins generated by Amberlite IRP-64<sup>®</sup> **2.17a** using H<sub>2</sub>SO<sub>4</sub> and H<sub>2</sub>O<sub>2</sub> 30 wt. % at 50 °C



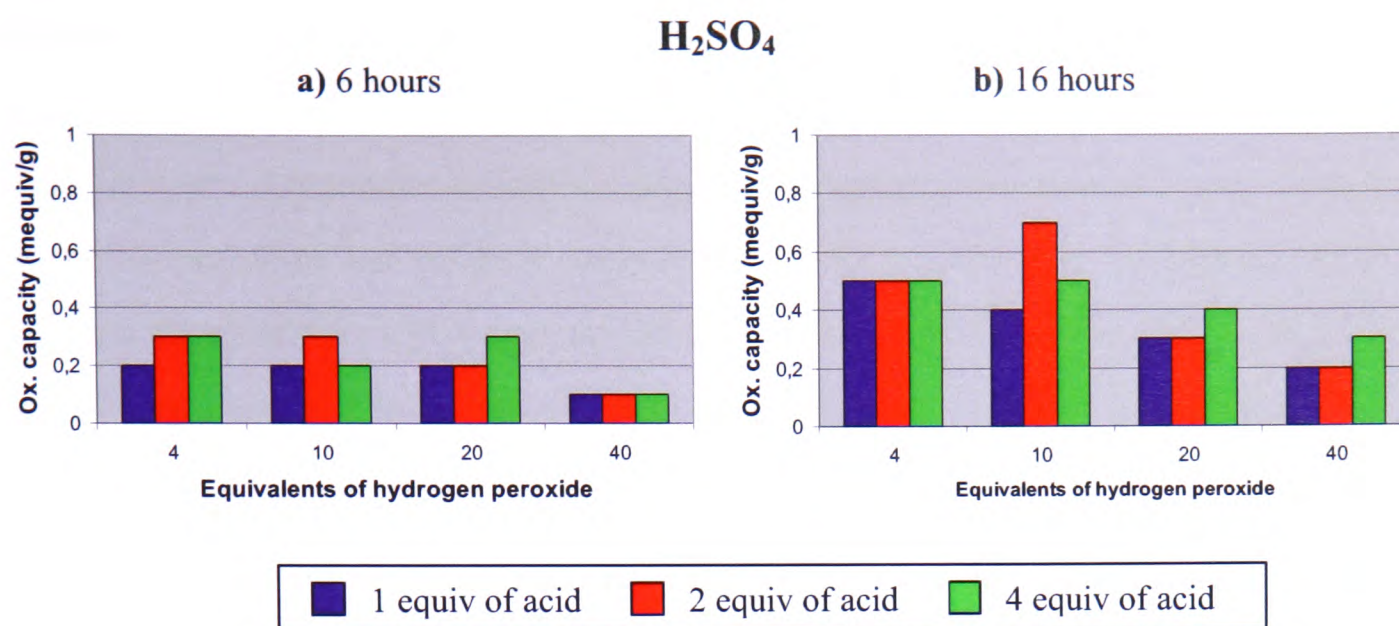
**Graph 2. 5** Activity of the peracid resins generated by Amberlite IRP-64<sup>®</sup> **2.17a** using PTSA and H<sub>2</sub>O<sub>2</sub> 30 wt. % at 50 °C



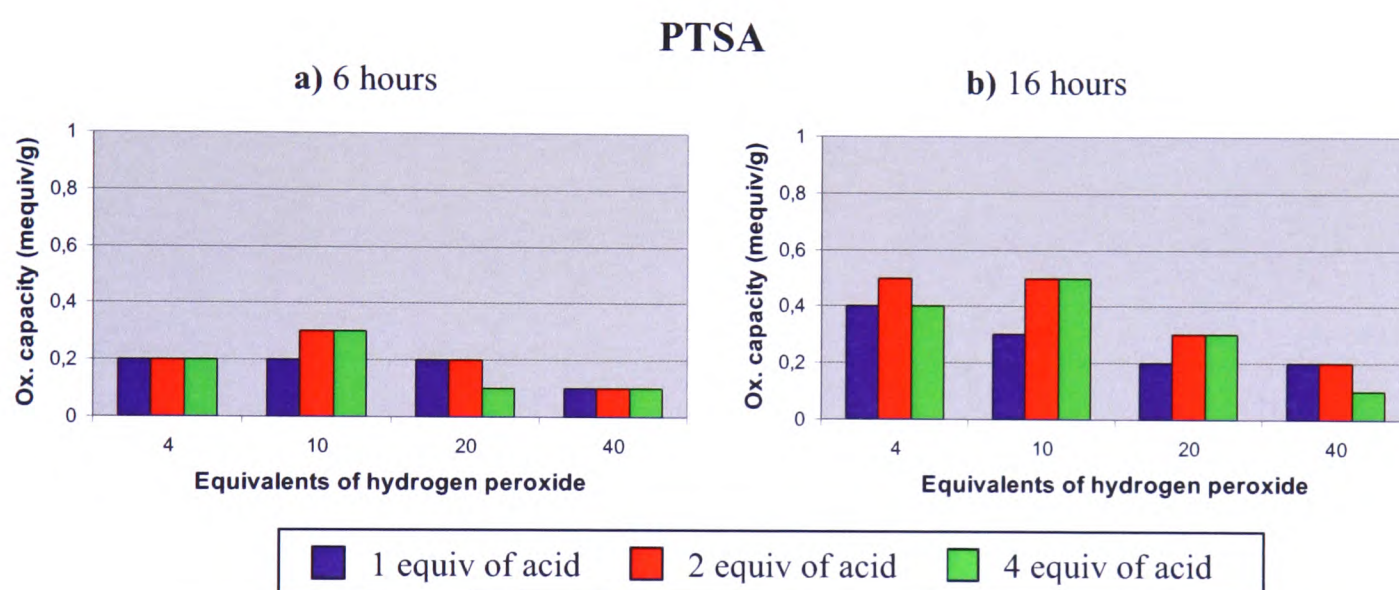
**Graph 2. 6** Activity of the peracid resins generated by Amberlite IRP-64<sup>®</sup> **2.17a** using MA and H<sub>2</sub>O<sub>2</sub> 30 wt. % at 50 °C

Another cycle of experiments was performed using Amberlite IRP-64<sup>®</sup> **2.17a**, in this case it was decided to use more drastic oxidising conditions. The resin was stirred in a solution of 50 wt. % hydrogen peroxide at 50 °C for 16 hours, in the presence of strong acids. The use of 50 wt. % hydrogen peroxide showed some improvement in the oxidation capacity, but still the level of the percarboxylic groups on the resin remained low. Better oxidation capacity values were obtained heating the resin for 16 hours with 2 equiv of sulfuric or methanesulfonic acid and 4 or 10 equiv of hydrogen peroxide (Graph 2.7b, 2.9b).

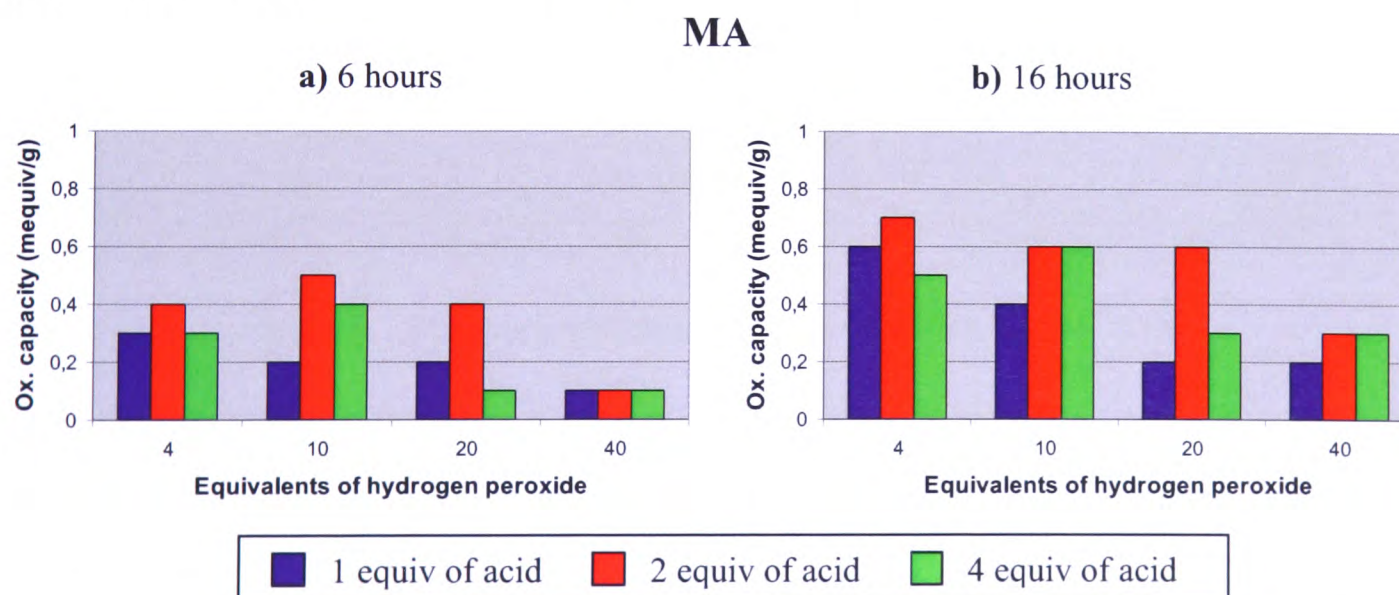




**Graph 2. 7** Activity of the peracid resins generated by Amberlite IRP-64<sup>®</sup> **2.17a** using H<sub>2</sub>SO<sub>4</sub> and H<sub>2</sub>O<sub>2</sub> 50 wt. % at 50 °C

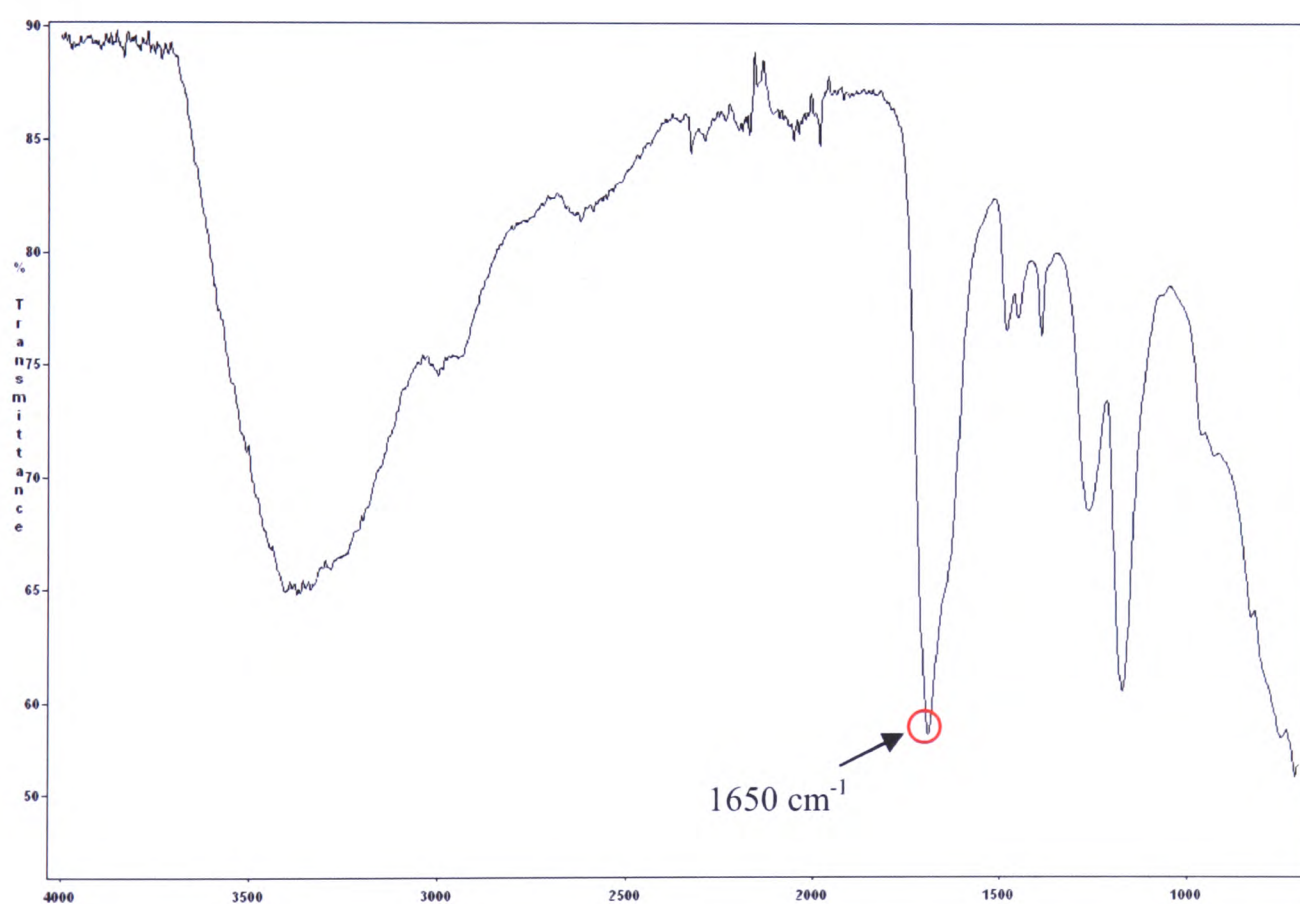


**Graph 2. 8** Activity of the peracid resins generated by Amberlite IRP-64<sup>®</sup> **2.17a** using PTSA and H<sub>2</sub>O<sub>2</sub> 50 wt. % at 50 °C



**Graph 2. 9** Activity of the peracid resins generated by Amberlite IRP-64<sup>®</sup> **2.17a** using MA and H<sub>2</sub>O<sub>2</sub> 50 wt. % at 50 °C

Attempts to increase the temperature from 50 °C to 70 °C gave lower conversions; in fact, high temperature conditions can speed up the decomposition of hydrogen peroxide and decrease the oxidative capacity. In general the use of a large excess of hydrogen peroxide led to poor conversions; this is probably correlated with the volumes involved (40 equiv correspond to 226 mL of H<sub>2</sub>O<sub>2</sub> 30 wt. % versus 113 mL H<sub>2</sub>O<sub>2</sub> 50 wt. %), that increases the dilution of all other reagents and bring down the oxidative capacity of the resulted mixture. Samples of oxidised Amberlite IRP-64<sup>®</sup> **2.18a** were analysed by infrared spectroscopy, but the characteristic carbonyl absorption band at 1747-1748 cm<sup>-1</sup> of the oxidised carboxylic groups<sup>115</sup> was not observed (Figure 2.7). The general poor performances obtained with Amberlite IRP-64<sup>®</sup> could be explained mainly by the low functionalisable surface per gram of the resin.



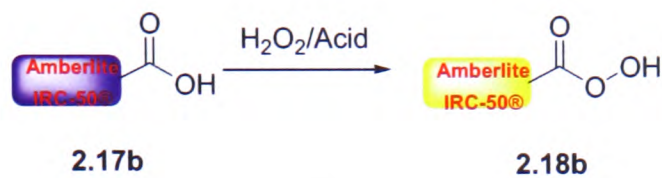
**Figure 2. 7** Infrared spectrum of oxidised Amberlite IRP-64<sup>®</sup> **2.18a**

#### **2.4. 4 Oxidation of Amberlite IRC-50<sup>®</sup>**

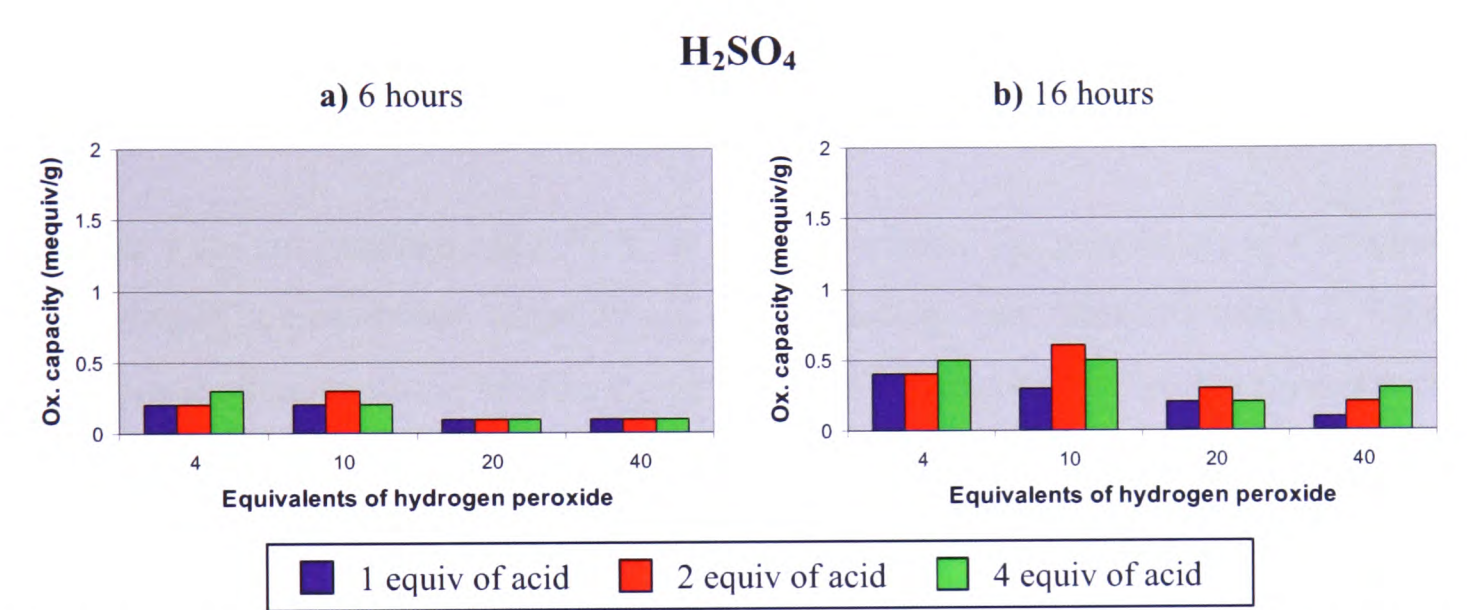
The experiments described above for Amberlite IRP-64<sup>®</sup> **2.17a** were performed also using Amberlite IRC-50<sup>®</sup> **2.17b** (Scheme 2.13). When this resin was stirred for 16 hours at 30 °C in the presence of 10 equiv of hydrogen 30 wt. % peroxide and with 2



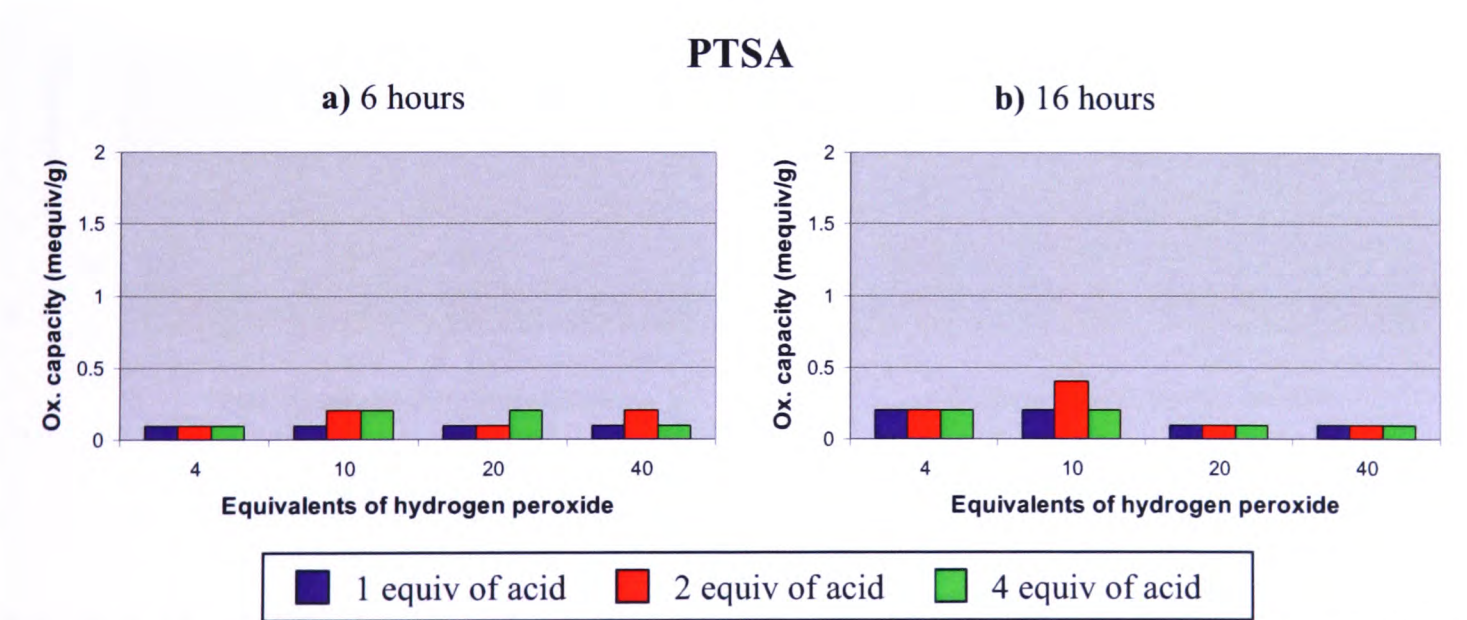
equiv of sulfuric or methanesulfonic acid an oxidation capacity of 0.6 mequiv/g was obtained (Graph 2.10b, Graph 2.12b). *P*-toluenesulfonic acid was less effective as a catalyst under these reaction conditions giving an oxidation capacity of 0.4 mequiv/g (Graph 2.11b).



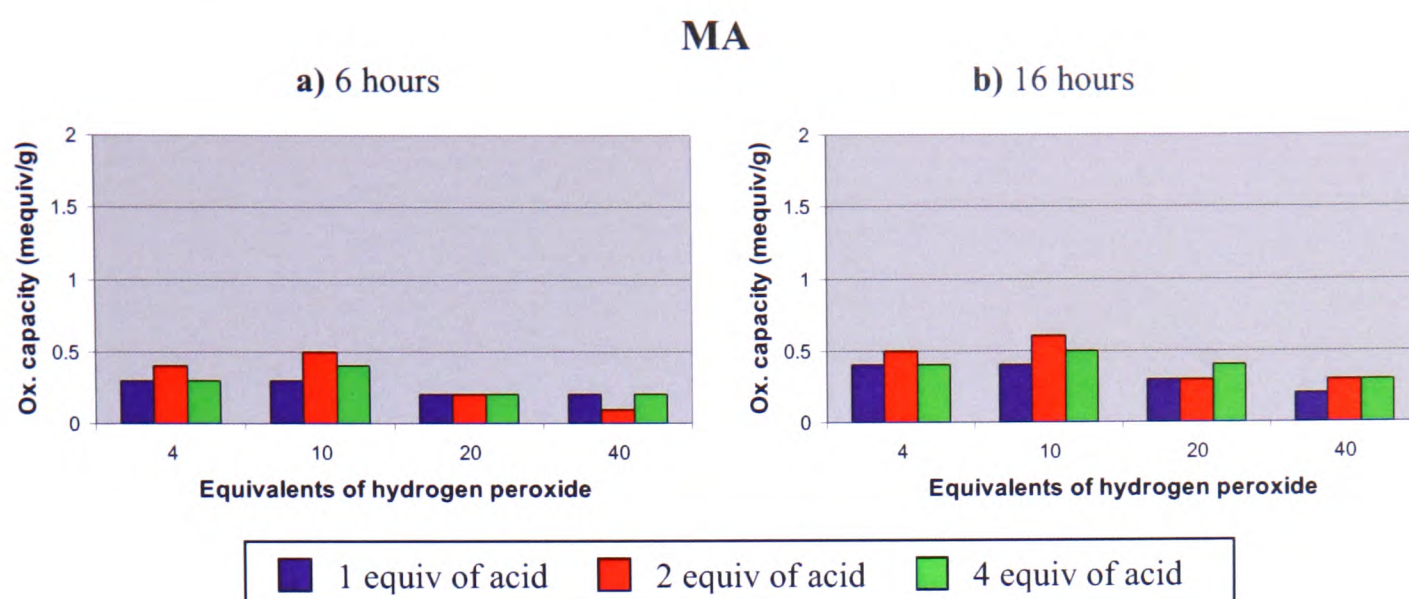
Scheme 2. 13 Oxidation of carboxylic resin Amberlite IRC-50<sup>®</sup> 2.17b



Graph 2. 10 Activity of the peracid resins generated by Amberlite IRC-50<sup>®</sup> 2.17b using H<sub>2</sub>SO<sub>4</sub> and H<sub>2</sub>O<sub>2</sub> 30 wt. % at 30 °C

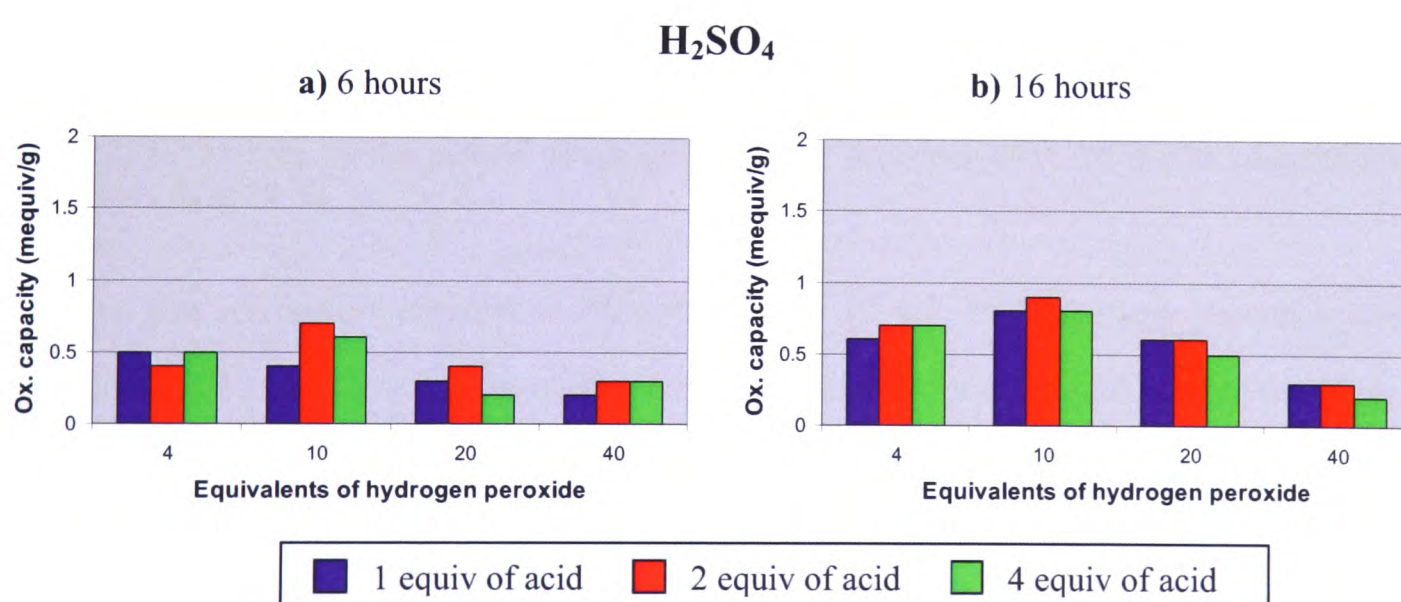


Graph 2. 11 Activity of the peracid resins generated by Amberlite IRC-50<sup>®</sup> 2.17b using PTSA and H<sub>2</sub>O<sub>2</sub> 30 wt. % at 30 °C



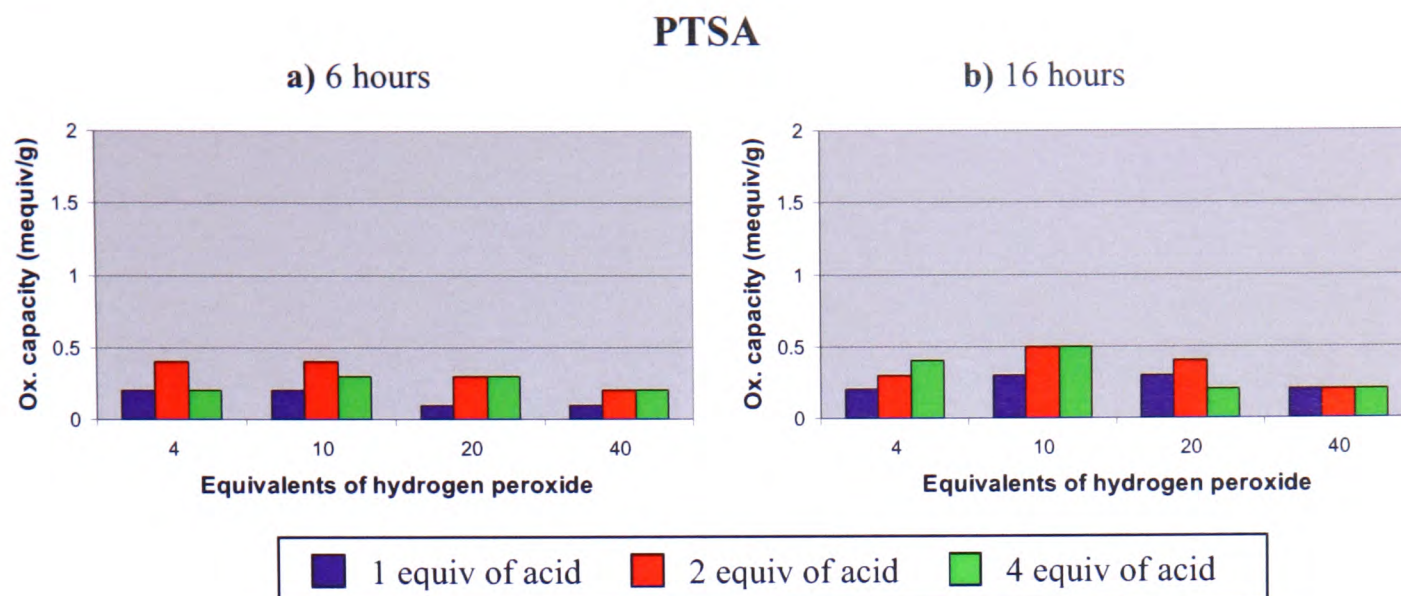
**Graph 2. 12** Activity of the peracid resins generated by Amberlite IRC-50<sup>®</sup> **2.17b** using MA and H<sub>2</sub>O<sub>2</sub> 30 wt. % at 30 °C

Changing the temperature from 30 °C to 50 °C increased the percentage of oxidation, for example an oxidation capacity of 0.9 mequiv/g was obtained using 2 equiv H<sub>2</sub>SO<sub>4</sub> or methanesulfonic acid in the presence of 10 equiv of hydrogen peroxide for 16 hours (Graph 2.13b, 2.15b). In the case of *p*-toluenesulfonic acid an increase in temperature was shown to be less effective and the best oxidation capacity value obtained was 0.5 mequiv/g (Graph 2.14b).

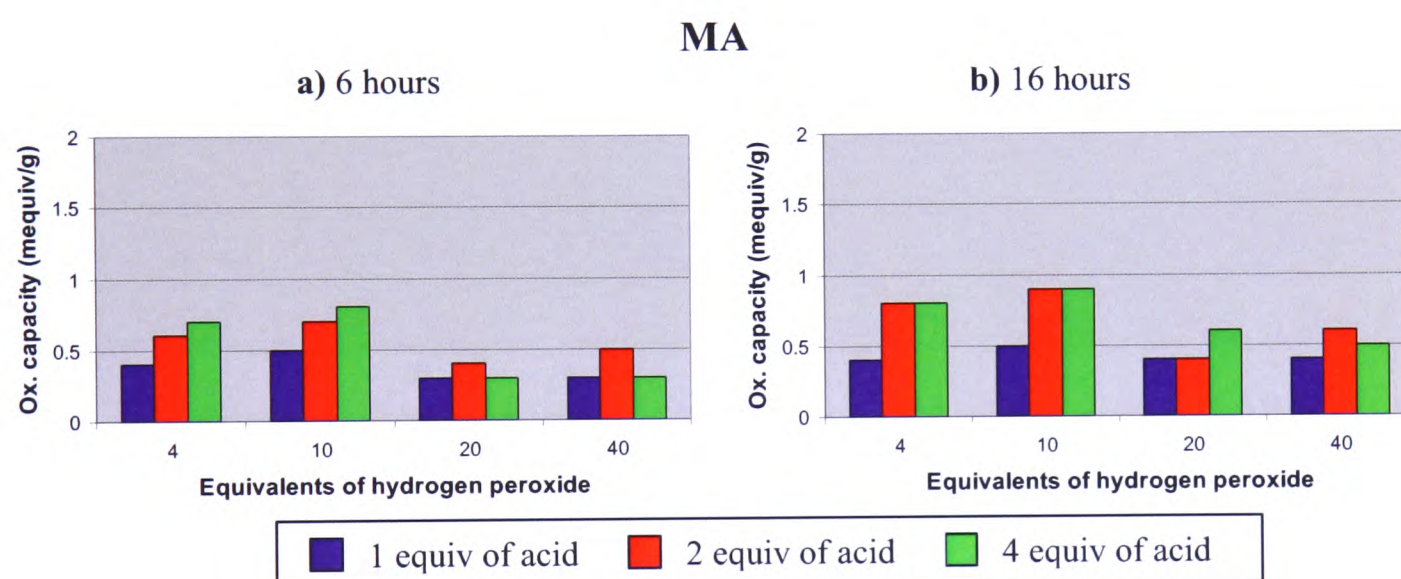


**Graph 2. 13** Activity of the peracid resins generated by Amberlite IRC-50<sup>®</sup> **2.17b** using H<sub>2</sub>SO<sub>4</sub> and H<sub>2</sub>O<sub>2</sub> 30 wt. % at 50 °C





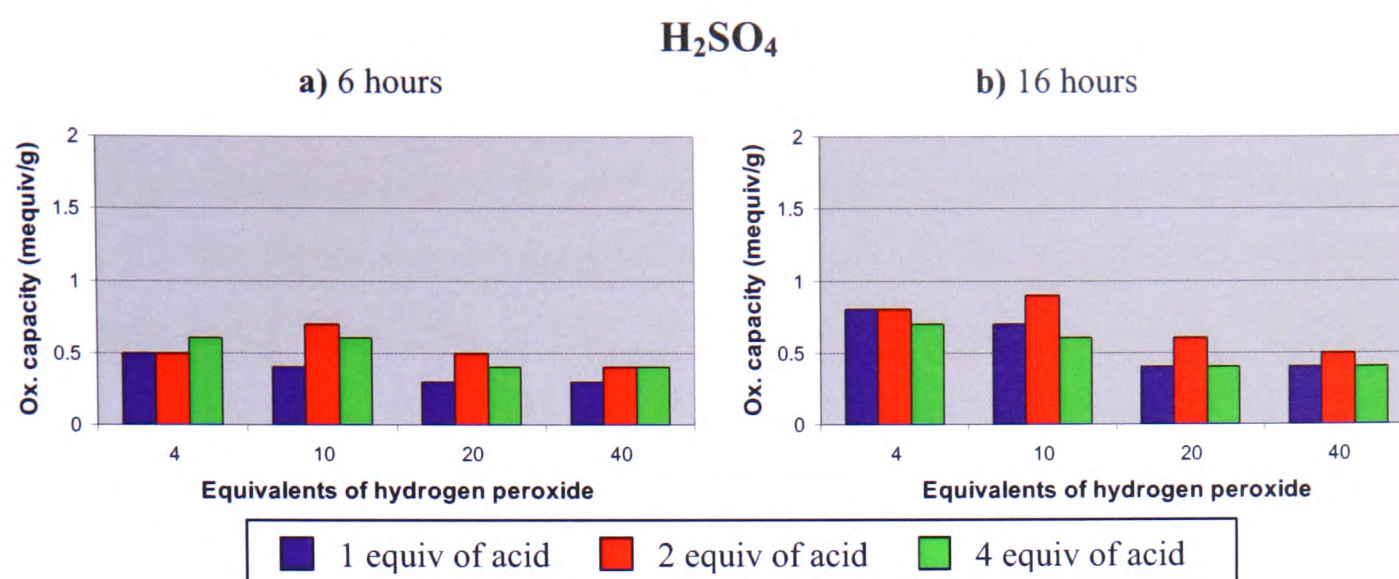
**Graph 2. 14** Activity of the peracid resins generated by Amberlite IRC-50<sup>®</sup> **2.17b** using PTSA and H<sub>2</sub>O<sub>2</sub> 30 wt. % at 50 °C



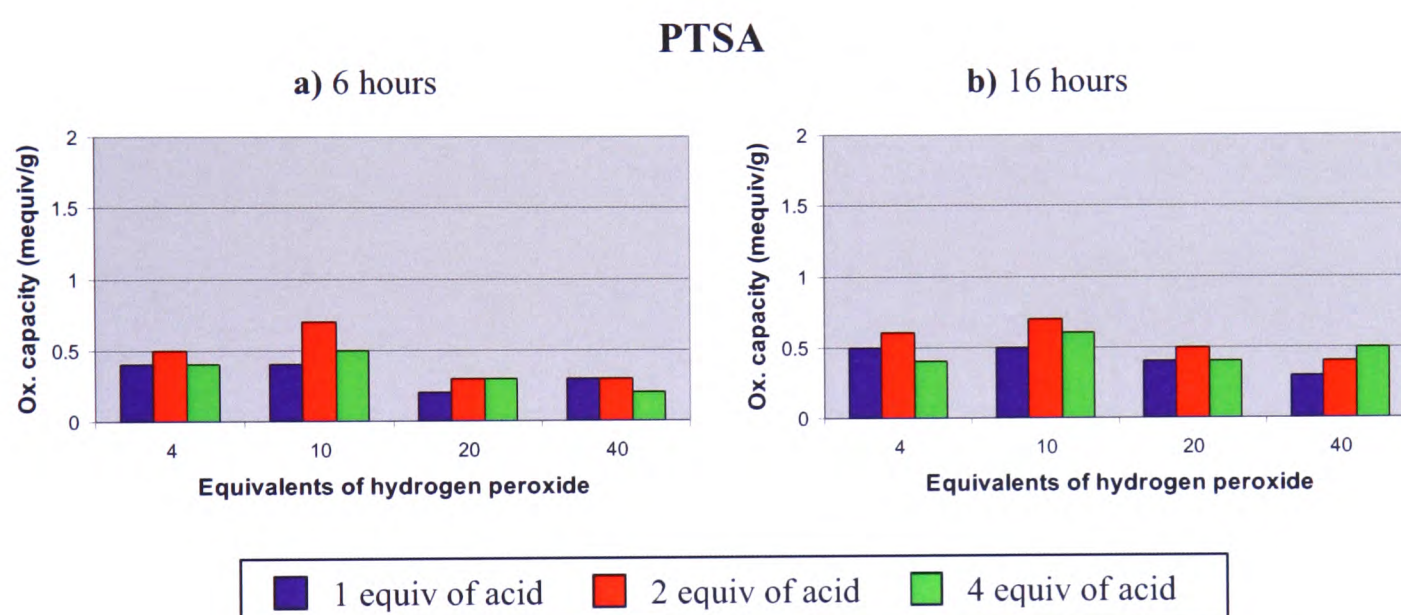
**Graph 2. 15** Activity of the peracid resins generated by Amberlite IRC-50<sup>®</sup> **2.17b** using MA and H<sub>2</sub>O<sub>2</sub> 30 wt. % at 50 °C

Because the oxidation capacities obtained with 30 wt. % hydrogen peroxide were inferior at 1.0 mequiv/g (10% of the oxidable groups in the resin), a new series of experiments using 50 wt. % hydrogen peroxide were performed. Based on the previous experiments on the Amberlite IRP-64<sup>®</sup>, it was decided to use a temperature of 50 °C in order to observe the performances of the Amberlite IRC-50<sup>®</sup> under stronger oxidative conditions.

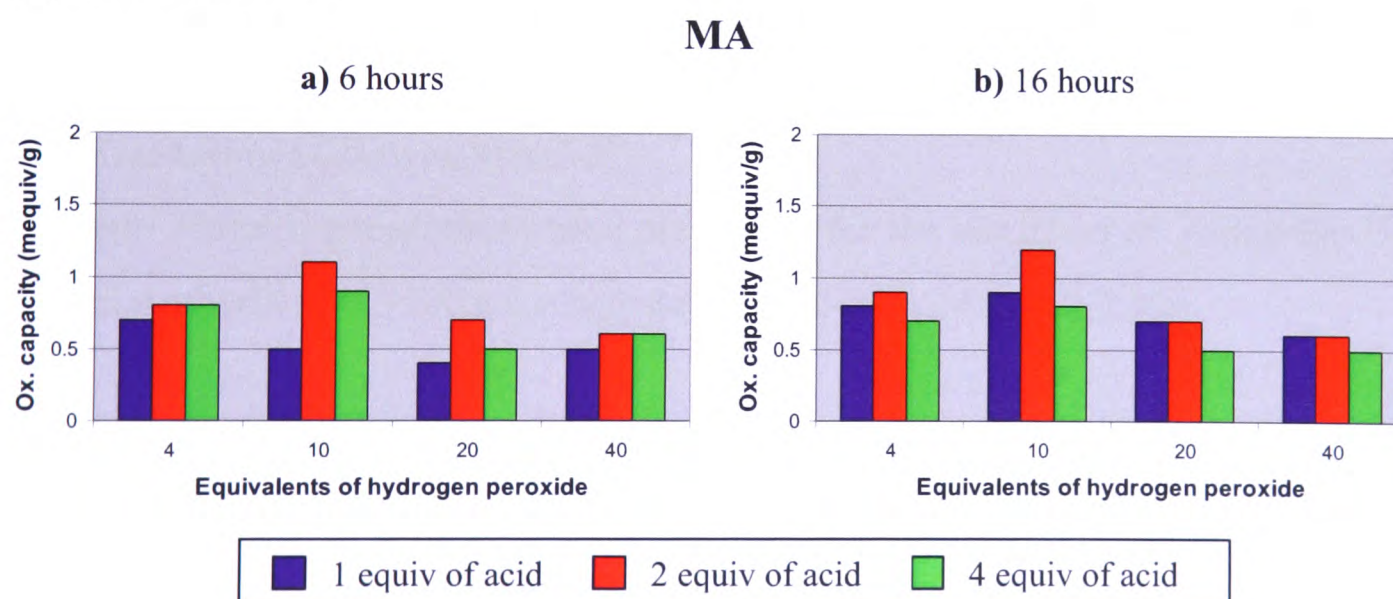




**Graph 2. 16** Activity of the peracid resins generated by Amberlite IRC-50<sup>®</sup> **2.17b** using H<sub>2</sub>SO<sub>4</sub> and H<sub>2</sub>O<sub>2</sub> 50 wt. % at 50 °C

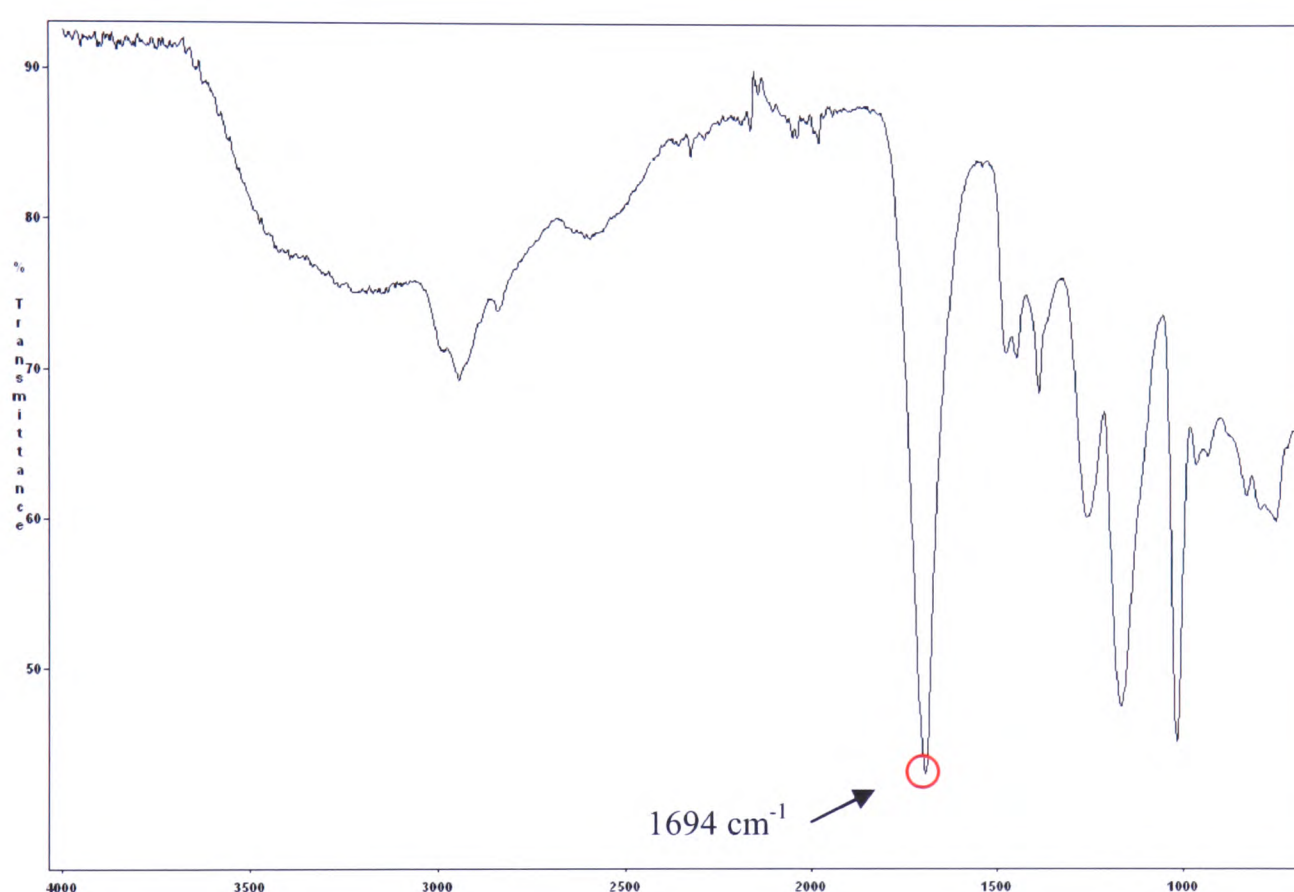


**Graph 2. 17** Activity of the peracid resins generated by Amberlite IRC-50<sup>®</sup> **2.17b** using PTSA and H<sub>2</sub>O<sub>2</sub> 50 wt. % at 50 °C



**Graph 2. 18** Activity of the peracid resins generated by Amberlite IRC-50<sup>®</sup> **2.17b** using MA and H<sub>2</sub>O<sub>2</sub> 50 wt. % at 50 °C

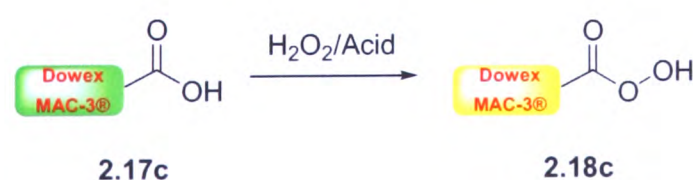
An oxidation capacity of 1.2 mequiv/g was obtained when 2 equiv of methanesulfonic were used in the presence of 10 equiv of peroxide (Graph 2.18). The infrared spectra did not show the peak of the oxidised carboxylic acid group at 1747-1748  $\text{cm}^{-1}$ , the signal was overlapped by the more intense signal of the unoxidised carboxylic acid (Figure 2.8). In fact, the oxidation of Amberlite IRC-50<sup>®</sup> **2.17b** with 50 wt. %  $\text{H}_2\text{O}_2$  was not effective and on an average the percentage of oxidised carboxylic groups was lower than 10%.



**Figure 2. 8** Infrared spectrum of oxidised Amberlite IRC-50<sup>®</sup> **2.18b**

#### 2.4. 5 Oxidation of Dowex MAC-3<sup>®</sup>

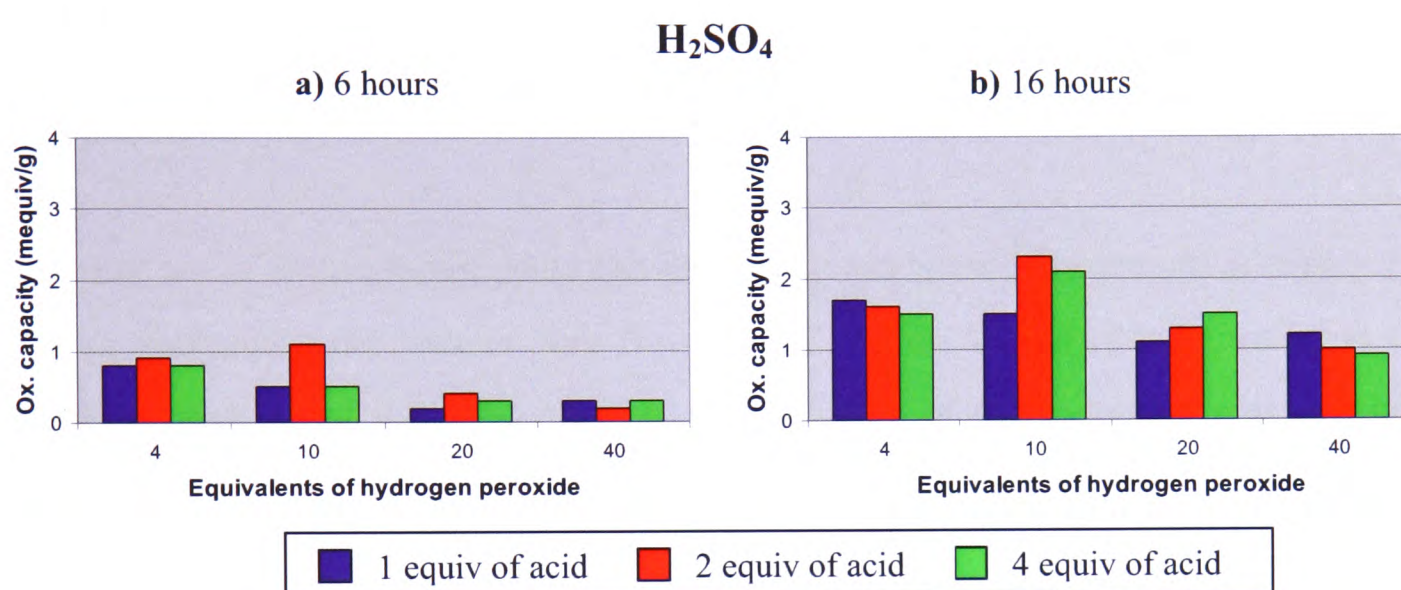
The same series of experiments used previously for the oxidation of Amberlite IRP-64<sup>®</sup> and Amberlite IRC-50<sup>®</sup> were repeated with Dowex MAC-3<sup>®</sup> **2.17c**.



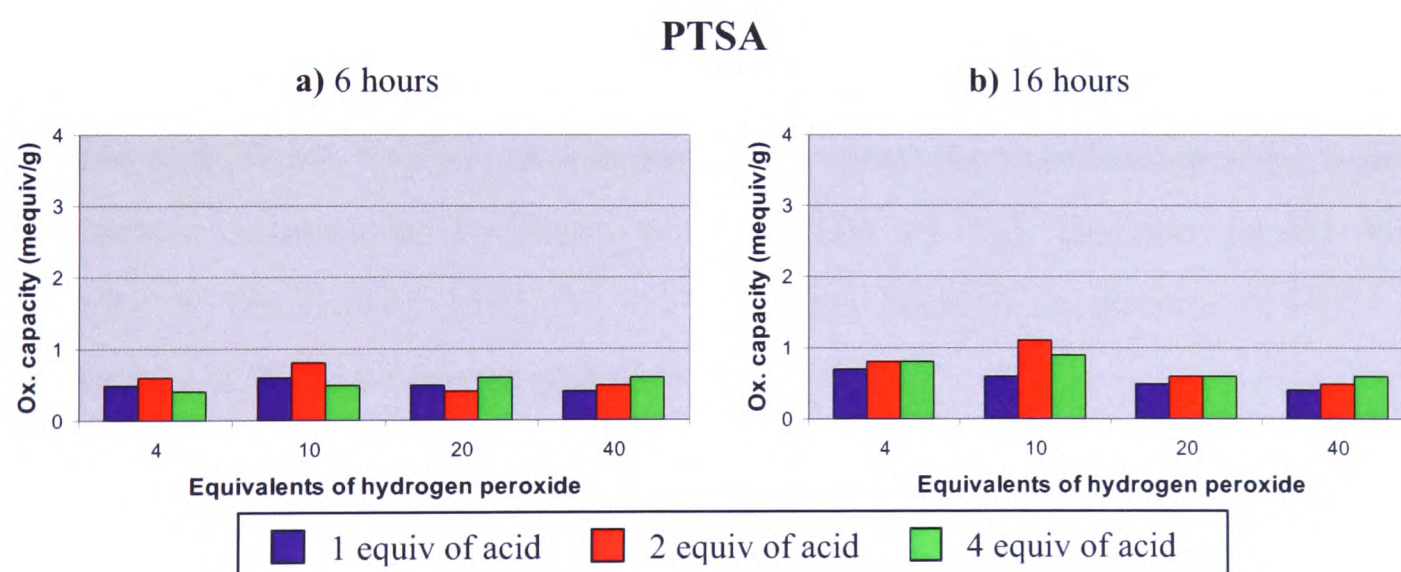
**Scheme 2. 14** Oxidation of carboxylic resin Dowex MAC-3<sup>®</sup> **2.17c**



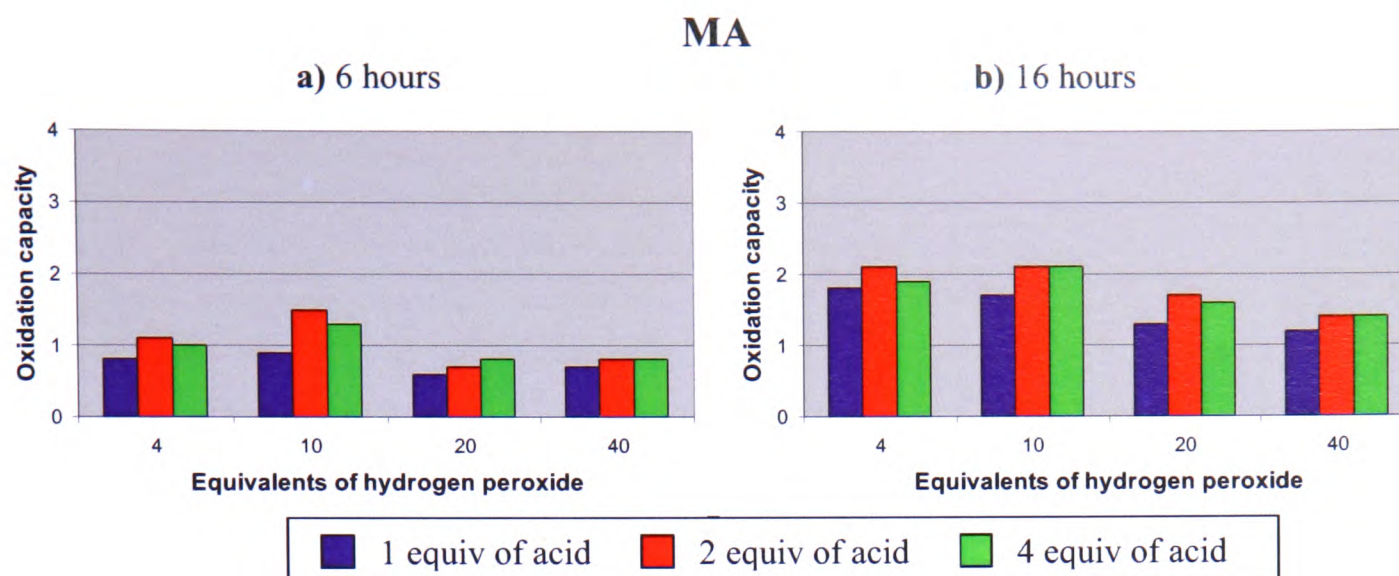
The results are reported in the graphs below and showed that this resin was more reactive towards oxidation. For example, using 2 equiv of  $\text{H}_2\text{SO}_4$  or methanesulfonic acid and 10 equiv 30 wt. % of  $\text{H}_2\text{O}_2$ , the oxidation capacity values increased up to 80% over the previous results achieved with Amberlite IRC-50<sup>®</sup> (Graph 2.19b, 2.21b). Reactions catalysed by *p*-toluenesulfonic acid were less effective; only in one case the percentage of percarboxylic acid groups was greater than 10% (Graph 2.20b).



**Graph 2. 19** Activity of the peracid resins generated by Dowex MAC-3<sup>®</sup> **2.17c** using  $\text{H}_2\text{SO}_4$  and  $\text{H}_2\text{O}_2$  30 wt. % at 30 °C



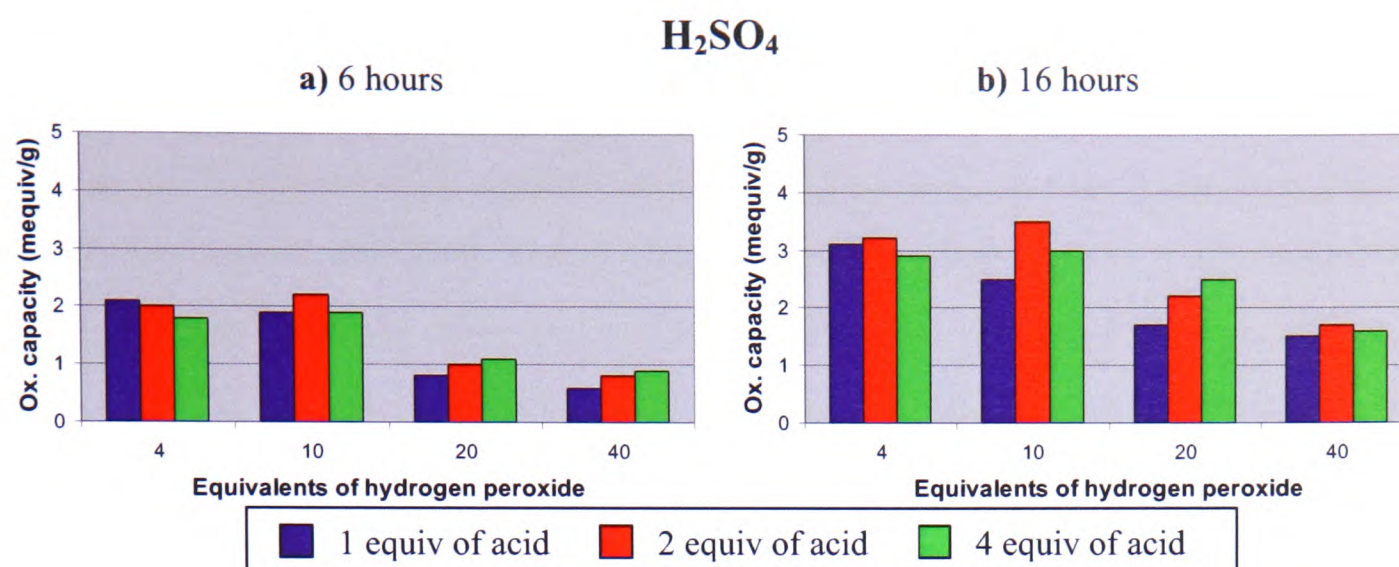
**Graph 2. 20** Activity of the peracid resins generated by Dowex MAC-3<sup>®</sup> **2.17c** using PTSA and  $\text{H}_2\text{O}_2$  30 wt. % at 30 °C



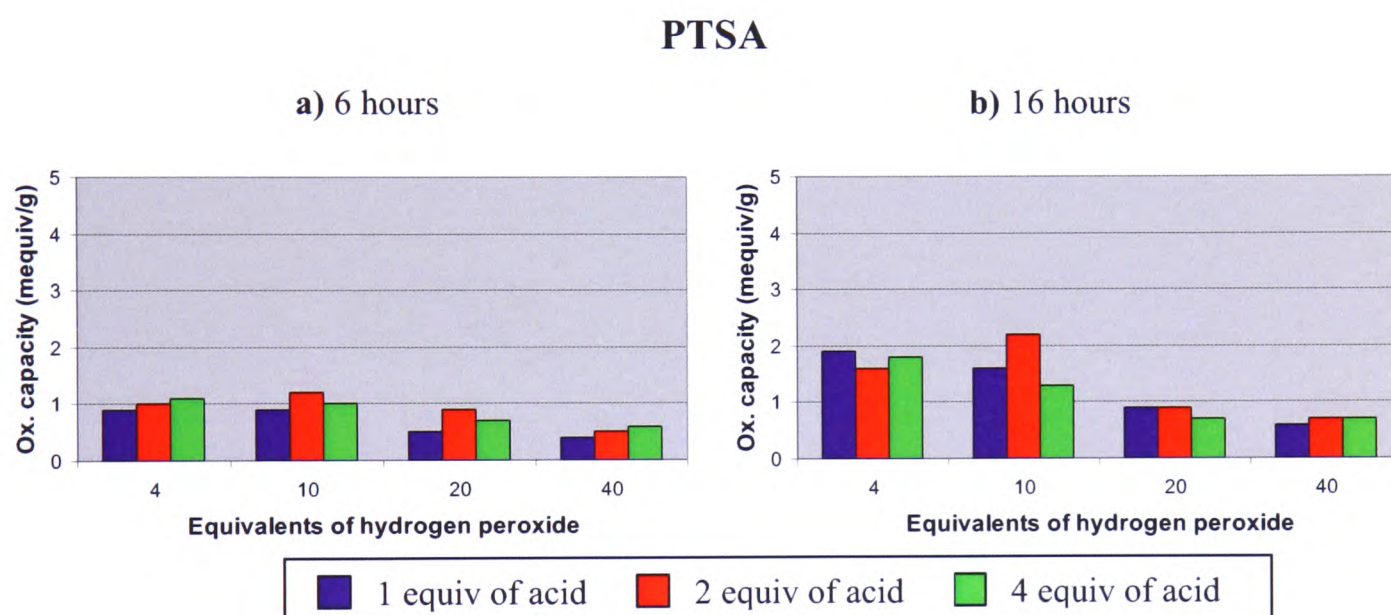
**Graph 2. 21** Activity of the peracid resins generated by Dowex MAC-3<sup>®</sup> **2.17c** using MA and H<sub>2</sub>O<sub>2</sub> 30 wt. % at 30 °C

A further set of experiments using the same concentration of hydrogen peroxide (30 wt. %), increasing the temperature from 30 °C to 50 °C, afforded a raise in the oxidation capacity of the final resin. In fact, a value of 4.2 mequiv/g was obtained when resin **2.17c** was oxidised using 2 equiv of methanesulfonic and 10 equiv of 30 wt. % H<sub>2</sub>O<sub>2</sub> for 16 hours at 50 °C (Graph 2.24b). This was the greatest oxidation capacity value obtained so far. The same experiments performed using a different acid (H<sub>2</sub>SO<sub>4</sub> and PTSA) gave inferior values of 4.0 mequiv/g (Graph 2.22, 2.23). Moreover, it was observed that all the oxidised resins with an oxidation capacity greater than 3.0 mequiv/g had a pale yellow colour. After these encouraging results obtained with 30 wt. % H<sub>2</sub>O<sub>2</sub>, it was decided to repeat the experiments using a more concentrated solution of hydrogen peroxide (50 wt. %). Because of the high reactivity of the Dowex MAC-3<sup>®</sup> **2.17c**, it was decided to perform a series of experiments at 30 °C before using higher temperatures.

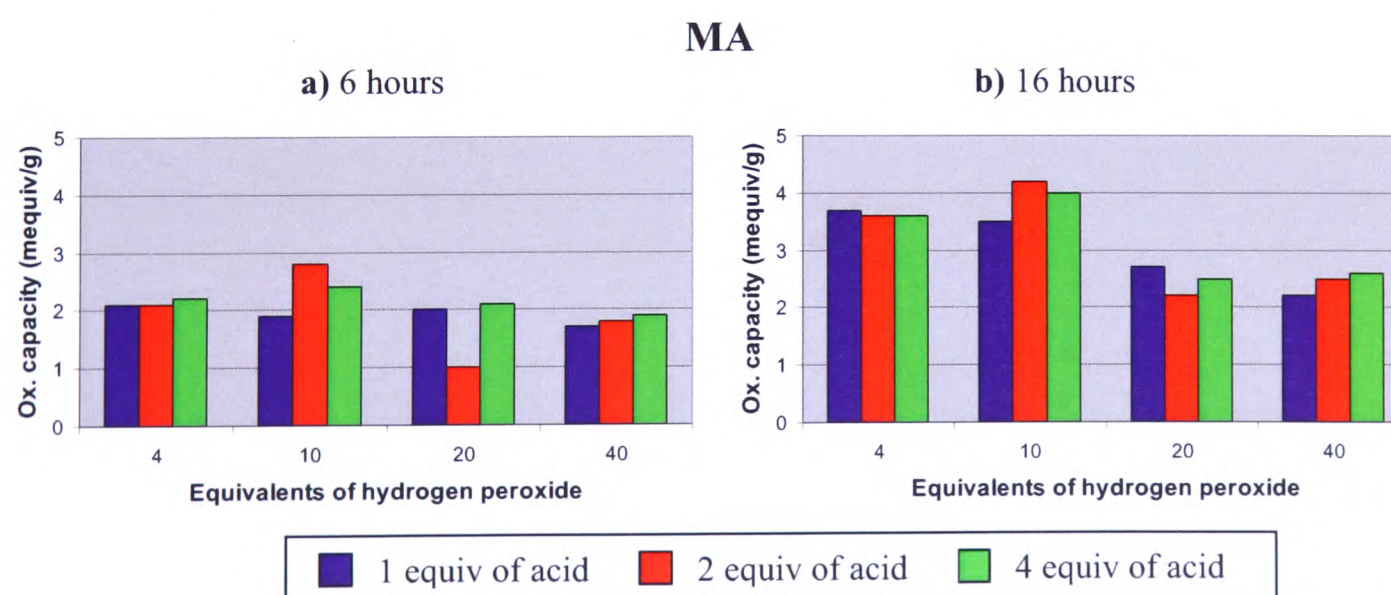




**Graph 2. 22** Activity of the peracid resins generated by Dowex MAC-3<sup>®</sup> **2.17c** using H<sub>2</sub>SO<sub>4</sub> and H<sub>2</sub>O, 30 wt. % at 50 °C



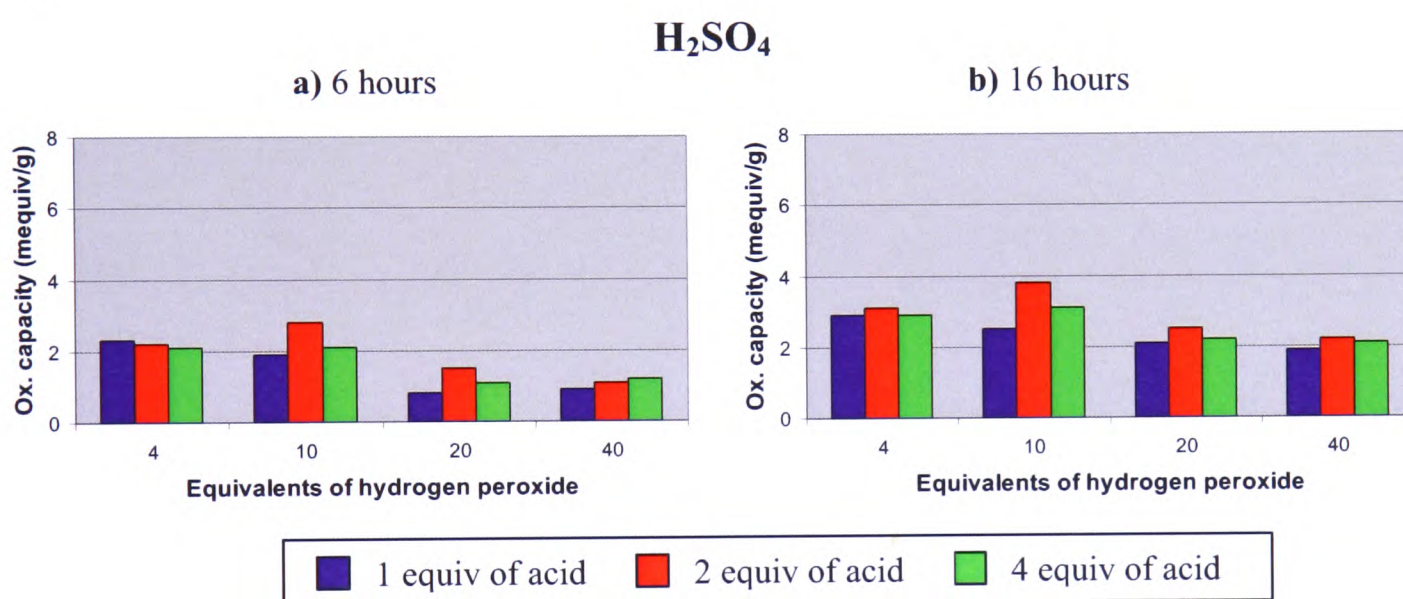
**Graph 2. 23** Activity of the peracid resins generated by Dowex MAC-3<sup>®</sup> **2.17c** using PTSA and H<sub>2</sub>O<sub>2</sub> 30 wt. % at 50 °C



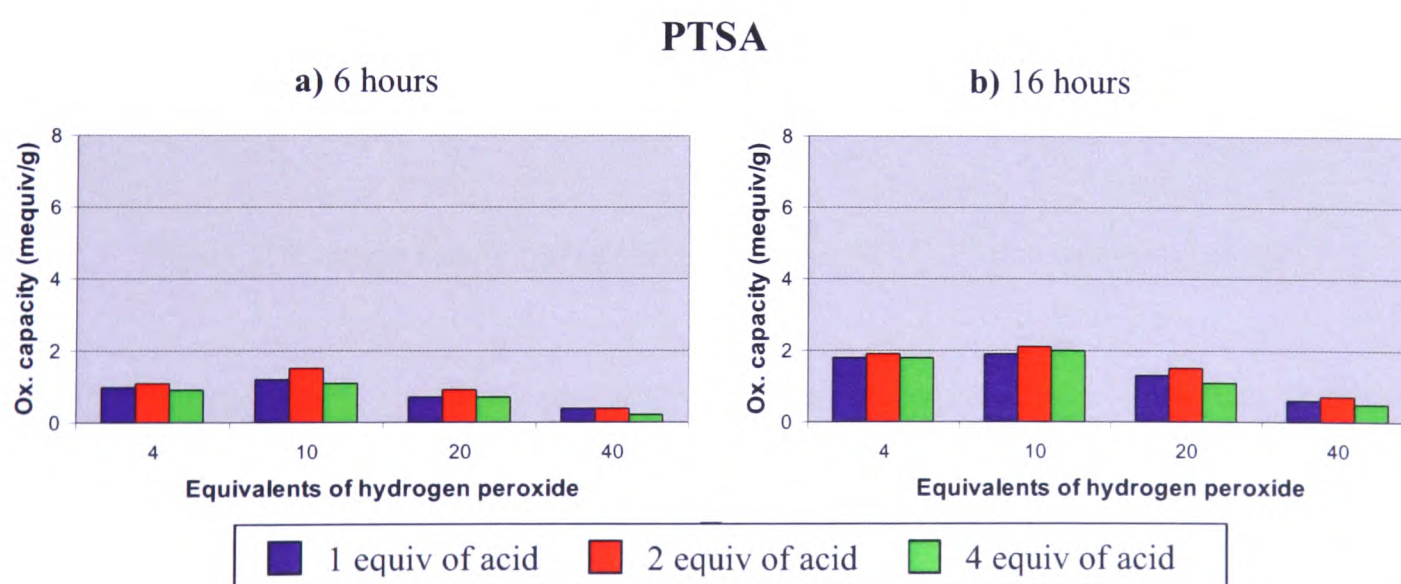
**Graph 2. 24** Activity of the peracid resins generated by Dowex MAC-3<sup>ic</sup> **2.17c** using MA and H<sub>2</sub>O<sub>2</sub> 30 wt. % at 50 °C



The first set of experiments were carried out using  $\text{H}_2\text{SO}_4$  as a catalyst, without obtaining significant improvements from the previous experiments with 30 wt. %  $\text{H}_2\text{O}_2$  at 50 °C (Graph 2.25 versus Graph 2.22), generally all the oxidation capacities were lower than 4 mequiv/g. The oxidation capacity values for the experiments with PTSA were comparable with those obtained from the experiments with 30 wt. %  $\text{H}_2\text{O}_2$  at 50 °C (Graph 2.26 versus Graph 2.23), with the best oxidation capacity of 2.1 mequiv/g. The highest oxidation capacity values (4.7 mequiv/g) were observed when Dowex MAC-3<sup>®</sup> **2.17c** was oxidised with 2 equiv of MA and 10 equiv of 50 wt. %  $\text{H}_2\text{O}_2$  (Graph 2.27b). The resin **2.18c** obtained was bright yellow, and infrared spectra showed a peak of the oxidised carboxylic acid group at 1744  $\text{cm}^{-1}$  (Figure 2.9).

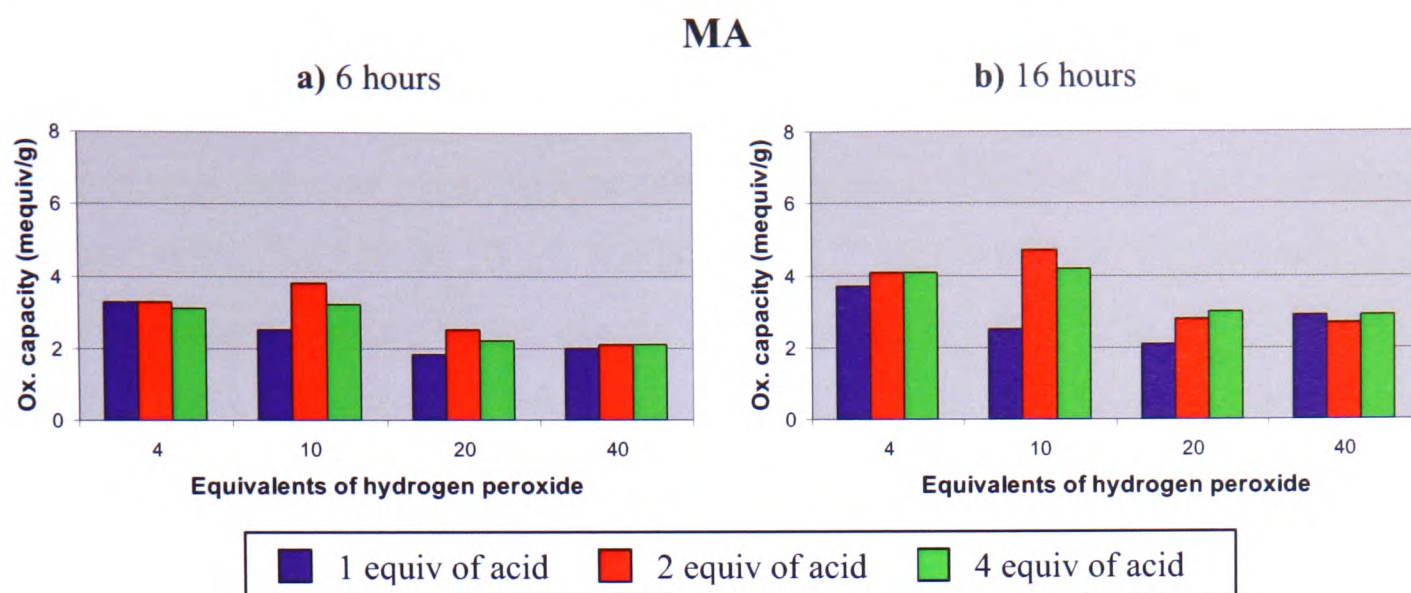


**Graph 2. 25** Activity of the peracid resins generated by Dowex MAC-3<sup>®</sup> **2.17c** using  $\text{H}_2\text{SO}_4$  and  $\text{H}_2\text{O}_2$  50 wt. % at 30 °C

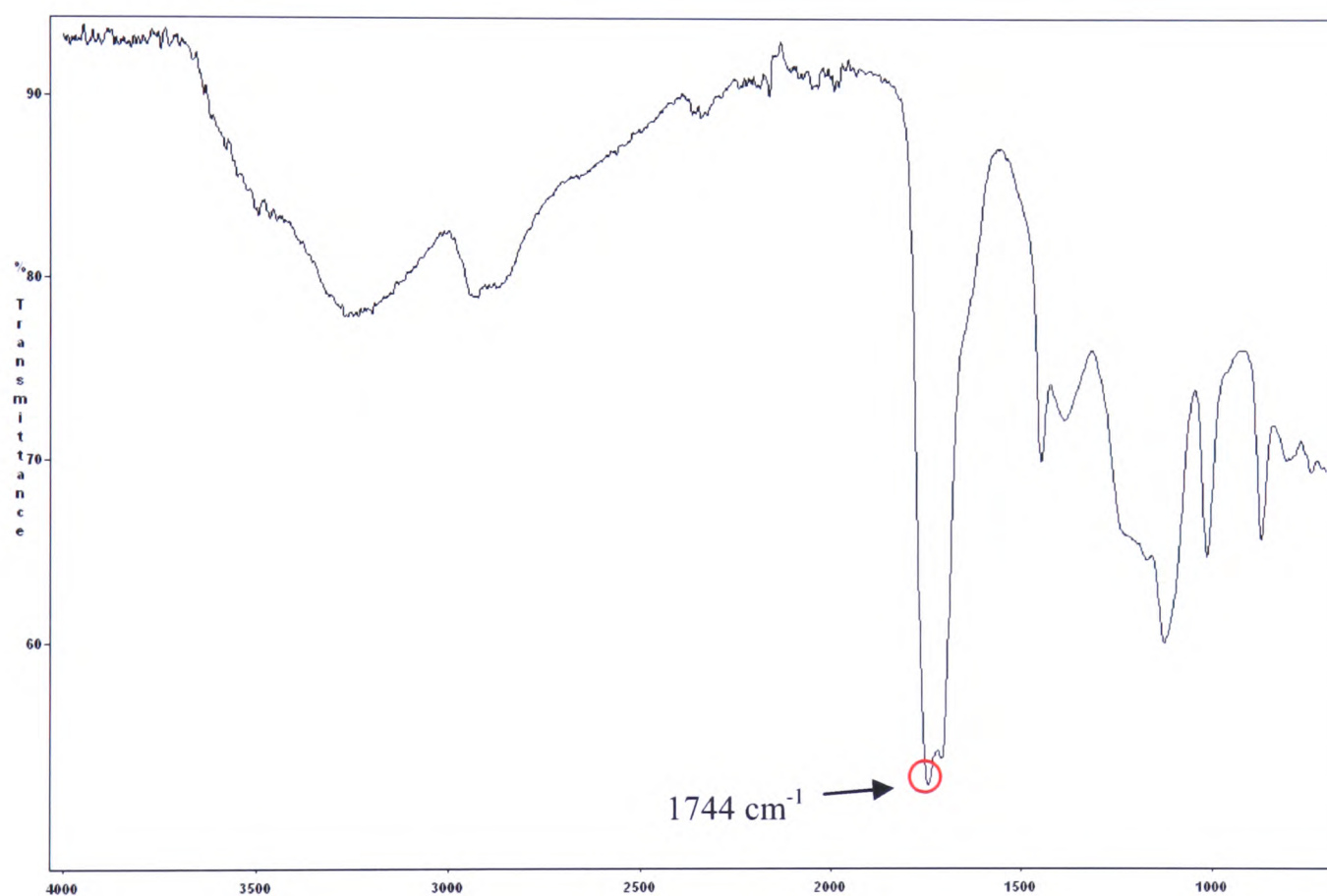


**Graph 2. 26** Activity of the peracid resins generated by Dowex MAC-3<sup>®</sup> **2.17c** using PTSA and  $\text{H}_2\text{O}_2$  50 wt. % at 30 °C





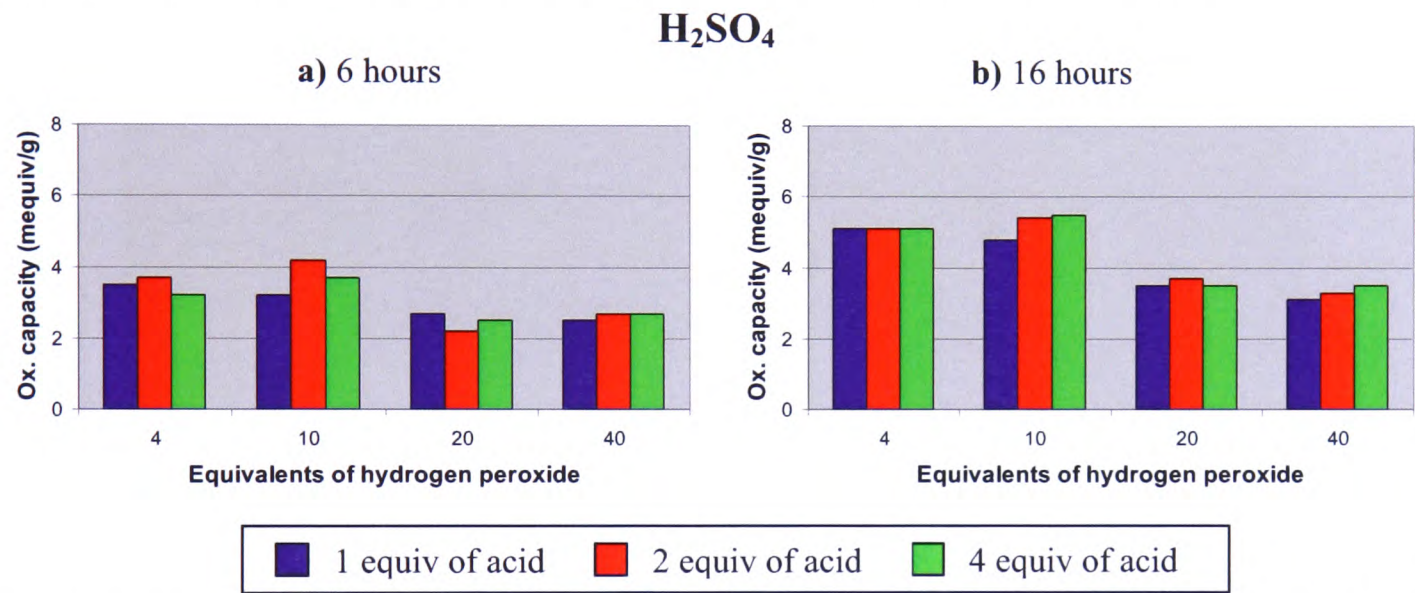
**Graph 2. 27** Activity of the peracid resins generated by Dowex MAC-3<sup>®</sup> **2.17c** using MA and H<sub>2</sub>O<sub>2</sub> 50 wt. % at 30 °C



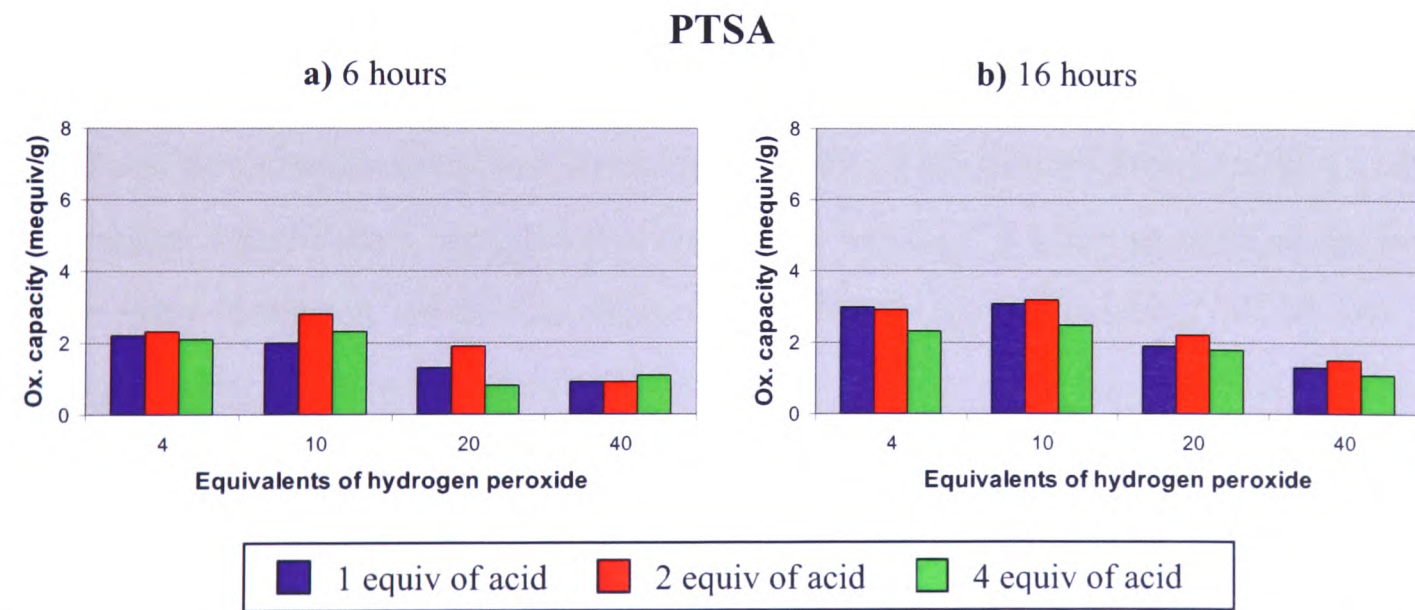
**Figure 2. 9** Infrared spectrum of oxidised Dowex MAC-3<sup>®</sup> (4.7 mequiv/g) **2.18c**

The mechanical stability of the dry resin and the absence of any exothermic effects during the reactions prompted a new series of experiments with 50 wt. % H<sub>2</sub>O<sub>2</sub> and the temperature of 50 °C. An oxidation capacity of 5.5 mequiv/g was observed when the resin was oxidised using 4 equiv of H<sub>2</sub>SO<sub>4</sub> and 10 equiv of 50 wt. % H<sub>2</sub>O<sub>2</sub>, this value was the highest oxidation capacity obtained with this catalyst during our

investigations (Graph 2.28b). A temperature of 50 °C also improved the oxidation capacity of the resin oxidised using PTSA as a catalyst (Graph 2.29b). MA has shown also in this case to be the best catalyst, the most effective oxidation conditions observed were: 2 equiv of 50 wt. %  $\text{H}_2\text{O}_2$  and 10 equiv of MA. In particular, an oxidation capacity value of 6.6 mequiv/g was obtained after 16 hours of treatment (Graph 2.30b). The dry resin was bright yellow (Figure 2.10) and the infrared spectra showed clearly the peak of the oxidised carboxylic acid group at 1747-1748  $\text{cm}^{-1}$ . Among all the resins used, the Dowex MAC-3<sup>®</sup> gave the highest oxidation capacity (6.6 mequiv/g) and it was decided to make further investigations, in order to optimise the oxidation procedure and to determine its stability and the reactivity.

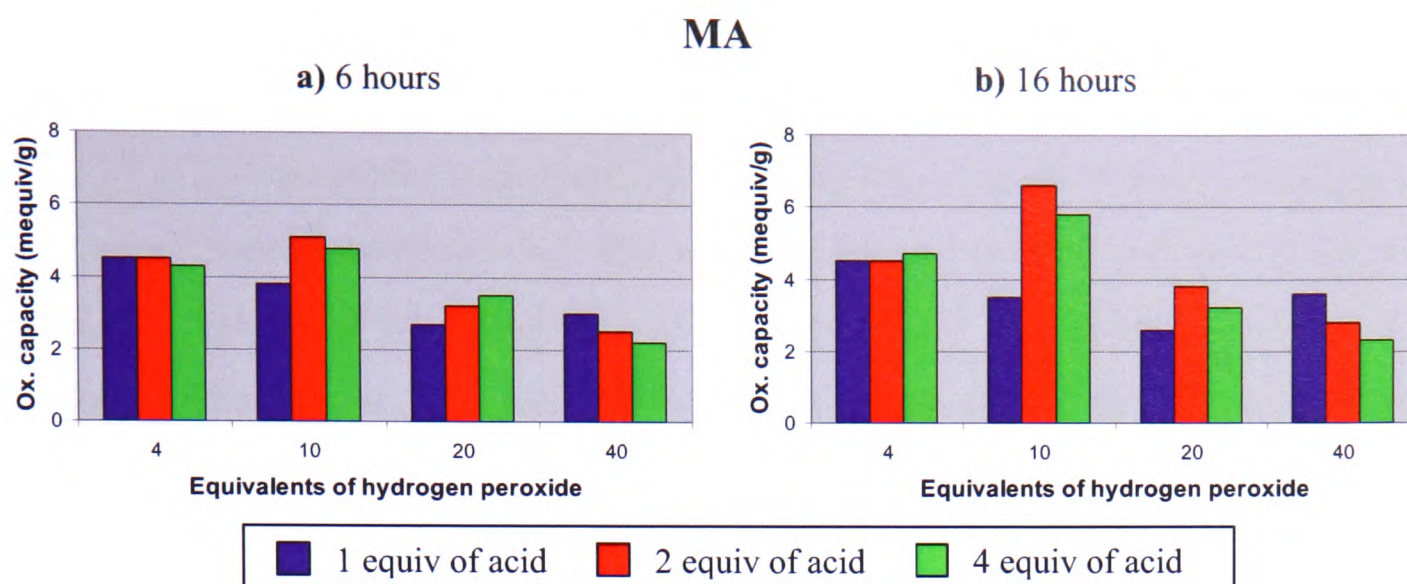


**Graph 2. 28** Activity of the peracid resins generated by Dowex MAC-3<sup>®</sup> **2.17c** using  $\text{H}_2\text{SO}_4$  and  $\text{H}_2\text{O}_2$  50 wt. % at 50 °C



**Graph 2. 29** Activity of the peracid resins generated by Dowex MAC-3<sup>®</sup> **2.17c** using PTSA and  $\text{H}_2\text{O}_2$  50 wt. % at 50 °C





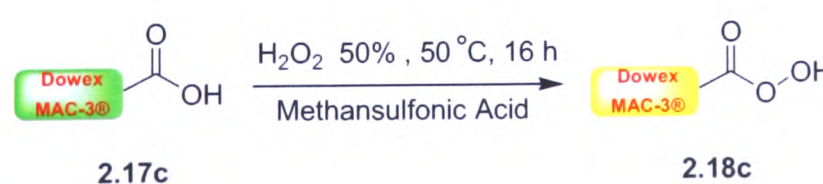
**Graph 2. 30** Activity of the peracid resins generated by Dowex MAC-3<sup>®</sup> **2.17c** using MA and H<sub>2</sub>O<sub>2</sub> 50 wt. % at 50 °C



**Figure 2. 10** Oxidised Dowex MAC-3<sup>®</sup> **2.18c**

## 2. 5 Synthesis optimisation and reactivity of oxidised Dowex MAC-3<sup>®</sup>

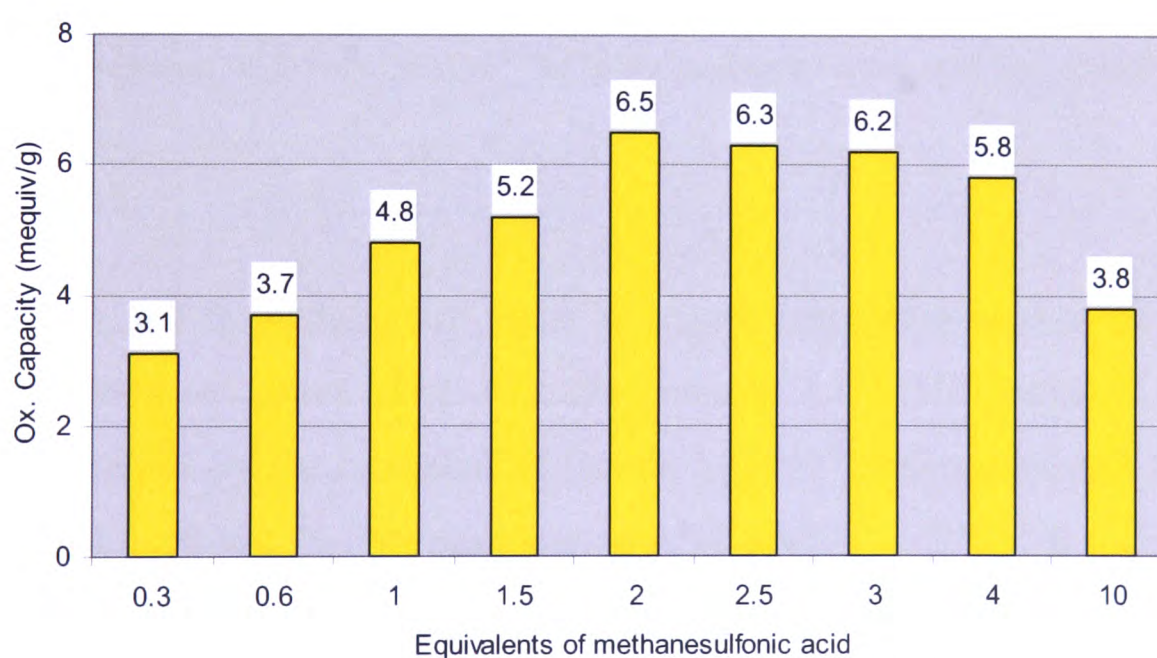
Preliminary experiments carried out with Dowex MAC-3<sup>®</sup> **2.17c** showed that the best results were obtained when the resin was oxidised with a solution of 50 wt. % hydrogen peroxide in water and methanesulfonic acid, at 50°C for 16 hours (Scheme 2.15).



**Scheme 2. 15** Oxidation of Dowex MAC-3<sup>®</sup>



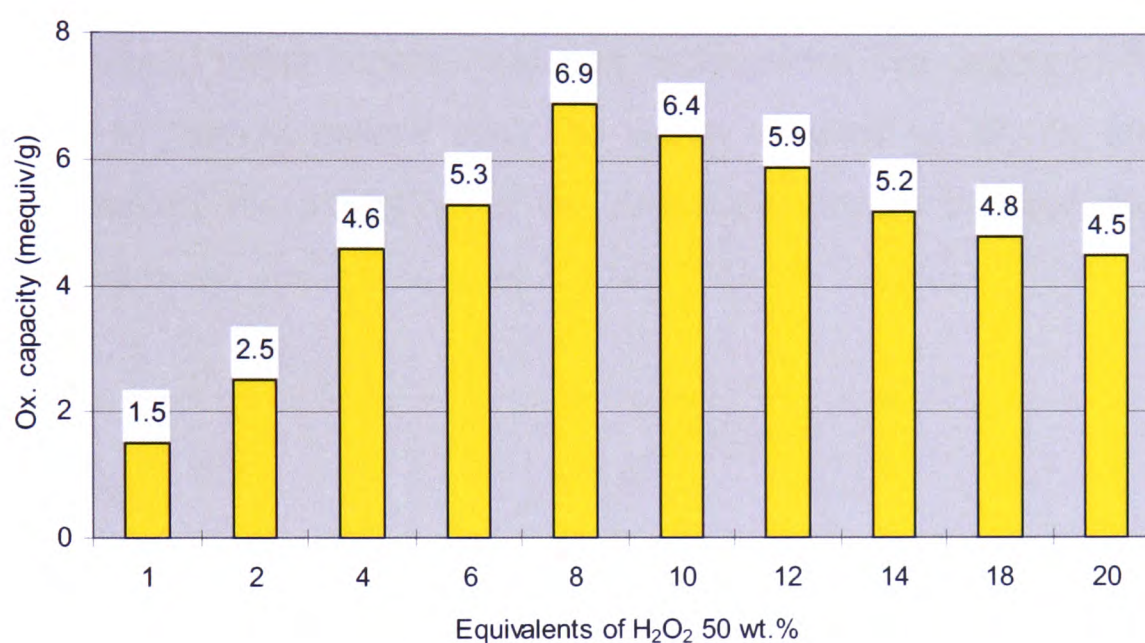
A new series of experiments were carried out to optimise the amount of 50 wt. %  $\text{H}_2\text{O}_2$  and MA required for the oxidation. In the first series of experiments Dowex MAC-3<sup>®</sup> (2 g) was stirred with 50 wt. %  $\text{H}_2\text{O}_2$  (10 equiv) at 50 °C for 16 hours in the presence of methanesulfonic acid. The amount of acid was varied from 0.3 equiv to 4.0 equiv. The resin was washed with methanol until the eluent was  $\text{H}_2\text{O}_2$  free (cerium sulfate/ferroin method),<sup>88</sup> and dried in vacuo for 16 h. The loading was evaluated by iodometric titration, as described before. The results reported in Graph 2.31 show how the oxidation capacity increases when changing the amount of methanesulfonic acid used. However this positive trend changed direction when the amount of methanesulfonic acid exceeded 3 equiv. The fall of oxidation capacity, when an excess of methanesulfonic acid was employed, could be explained by the fact that the acid is increasing the rate of decomposition of the hydrogen peroxide instead of promoting the oxidation of the resin. Because the oxidation capacity values remained almost unchanged when 2 or 3 equiv of methanesulfonic acid were used in the oxidation of the resin, it was decided that 2 equiv of methanesulfonic acid was the optimal amount of acid required to achieve the highest oxidation capacity with Dowex MAC-3<sup>®</sup>.



**Graph 2. 31** Oxidation of Dowex MAC-3<sup>®</sup> **2.17c** by  $\text{H}_2\text{O}_2$  50 wt. % by different amounts of methanesulfonic acid

A second series of experiments focused on optimising the quantity of  $\text{H}_2\text{O}_2$  (50 wt. %) used. Dowex MAC-3<sup>®</sup> was stirred with methanesulfonic acid (2 equiv) and  $\text{H}_2\text{O}_2$

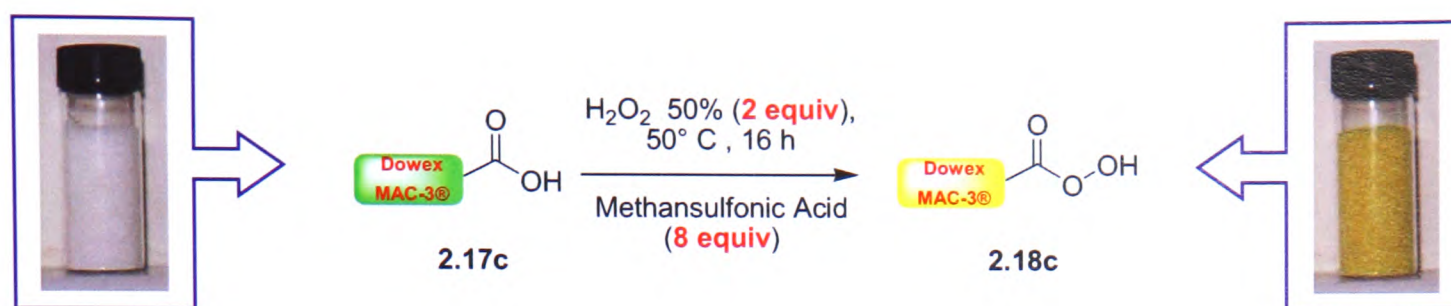
at 50 °C for 16 hours, and the amount of  $\text{H}_2\text{O}_2$  was varied from 1 to 20 equiv. The oxidation capacity values obtained are reported in Graph 2.32. It was observed that the oxidation capacity increased from 1.5 to 6.9 mequiv/g, while the peroxide varied from 1 to 8 equiv. This expected trend changed direction when more than 8 equiv of peroxide were employed. As observed before the excess of 50 wt. %  $\text{H}_2\text{O}_2$  causes an increase in the volume of solvent and consequently a decreasing in the concentration of methanesulfonic acid.



**Graph 2. 32** Oxidation of Dowex MAC-3<sup>®</sup> **2.17c** by methanesulfonic acid and different amounts  $\text{H}_2\text{O}_2$  50 wt. %

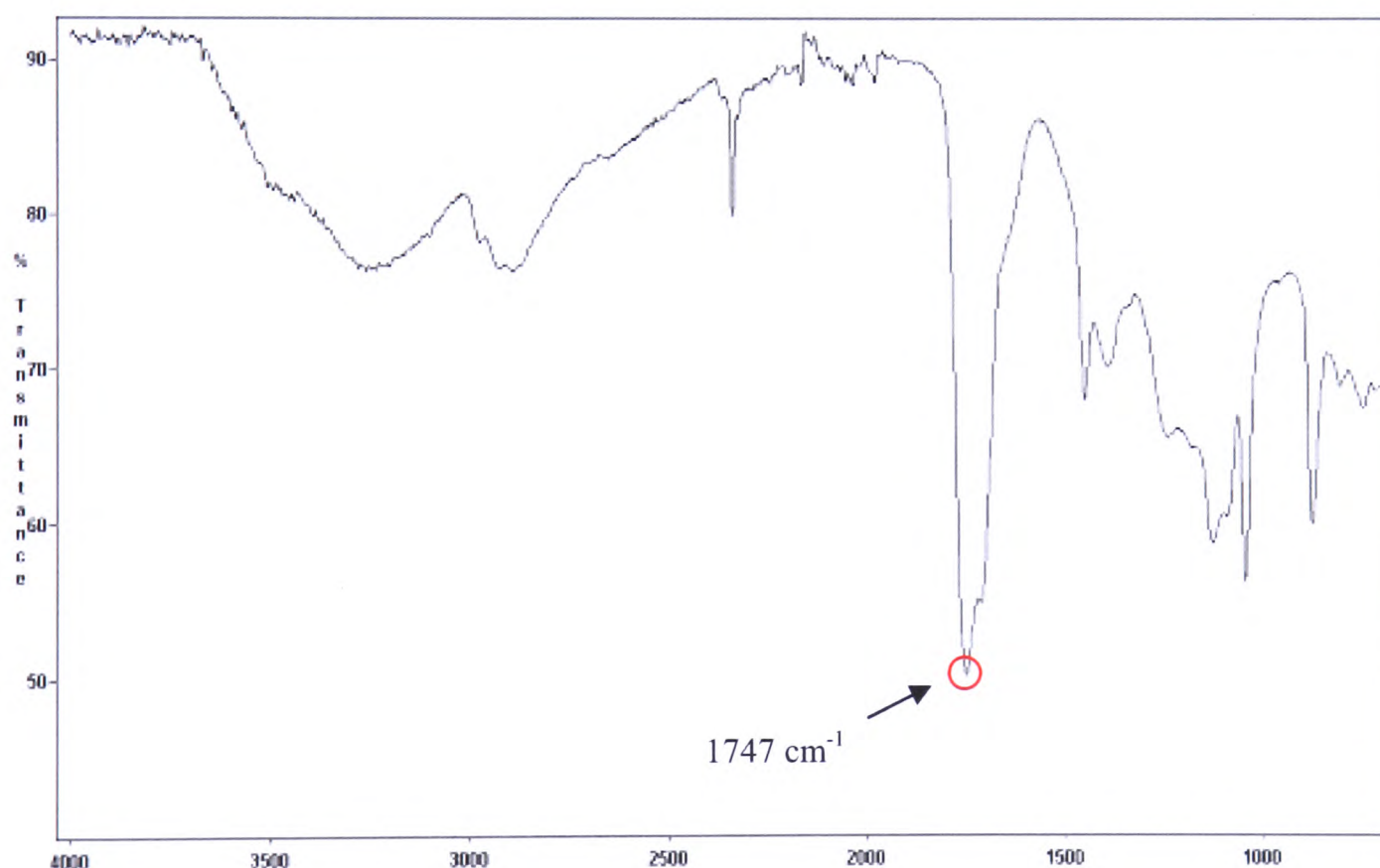
The data collected from these two series of experiments were used to develop the optimal oxidation of Dowex MAC-3<sup>®</sup> **2.17c** (Scheme 2.13). The percarboxylic resin **2.18c** was obtained by the treatment of Dowex MAC-3<sup>®</sup> with methanesulfonic acid (2 equiv) and a 50 wt. % hydrogen peroxide (8 equiv) at 50° C for 16 h. After oxidation a change in colour was observed, the resin beads became bright yellow (Scheme 2.16). The resin was washed with methanol until the eluent was  $\text{H}_2\text{O}_2$  free (cerium sulfate/ferroin indicator), and dried in vacuo for 16 h. The loading was evaluated by iodometric titration.





**Scheme 2. 16** Optimised oxidation of Dowex MAC-3<sup>®</sup> **2.17c**

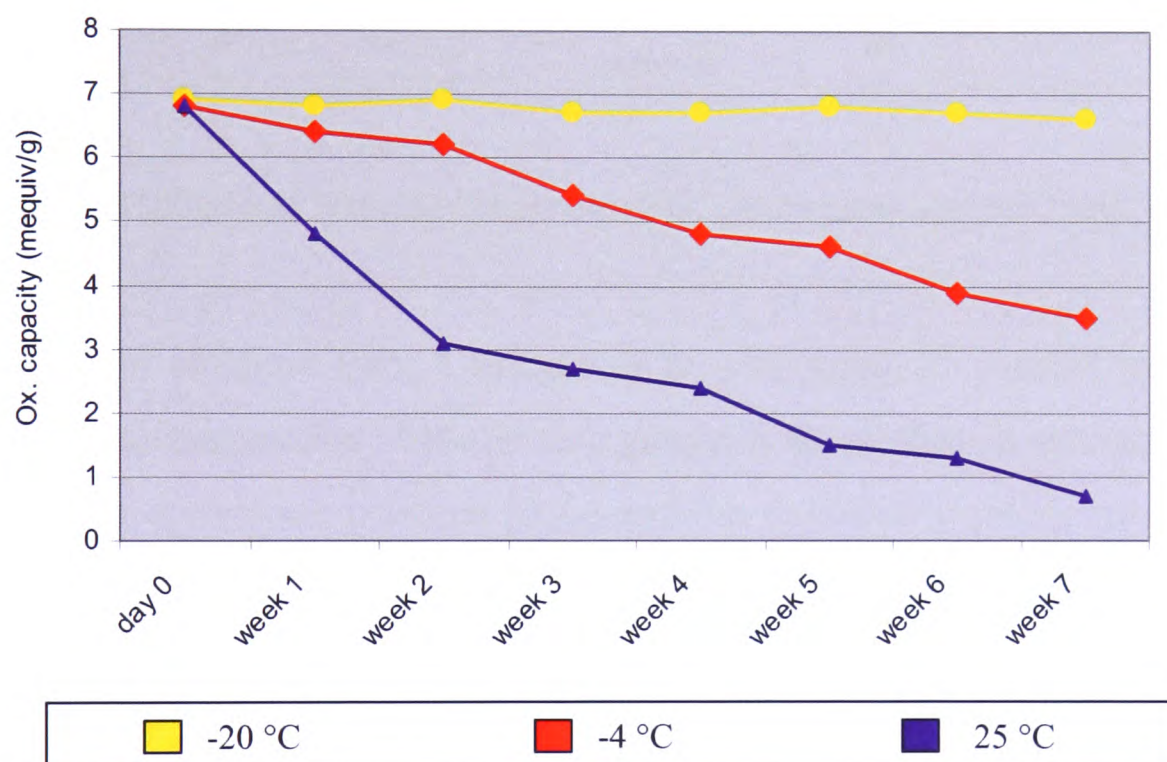
Dowex MAC-3<sup>®</sup> peracid resin **2.18c** gave a constant oxidation capacity (average value 6.7 mequiv/g) under various oxidation experiments. The degree of conversion of carboxylic to peracid groups could be easily detected by IR. In fact, it was possible to monitor the oxidation of the carboxylic groups by appearance of the characteristic carbonyl absorption band at 1747-1748  $\text{cm}^{-1}$  (Figure 2.11).



**Figure 2. 11** Infrared spectrum of peracid resin (6.7 mequiv/g) **2.18c**

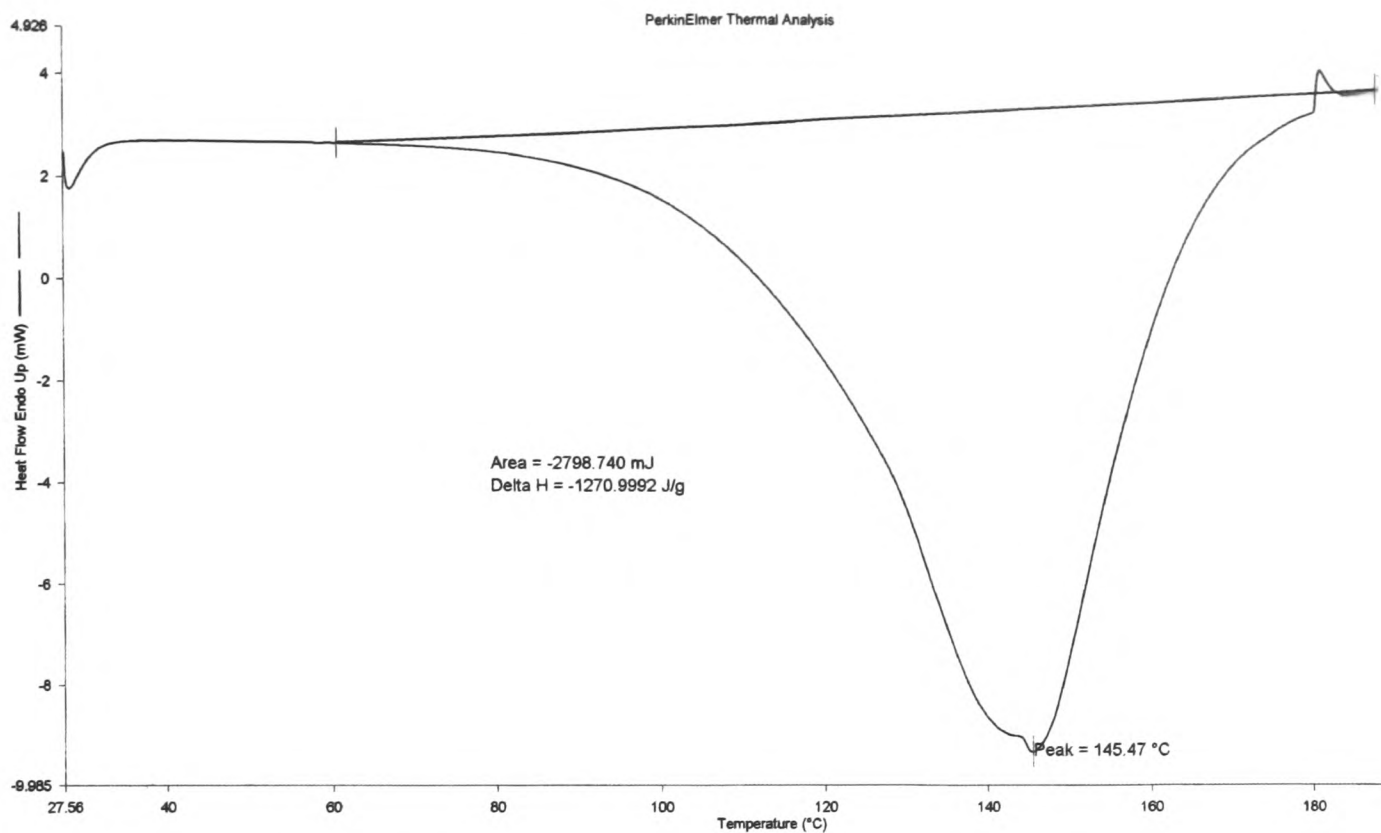
To test the stability of Dowex MAC-3<sup>®</sup> peracid resin **2.18c**, three samples of material were stored at different temperatures: firstly -20 °C (freezer), 4 °C (fridge) and room

temperature 25 °C (bench). All the resins were kept in the dark to protect them from the deteriorating action of the light on peracid. Every week the oxidation capacities of these three samples of Dowex MAC-3<sup>®</sup> peracid were determined by iodometric titration. The oxidation capacity of the peracid resins determined over 7 weeks is illustrated in Graph 2.33. It is clear that Dowex MAC-3<sup>®</sup> peracid resin **2.18c** was very stable if stored at -20 °C, on the contrary the oxidation capacity decreased when the resin was stored in the fridge, with an acceptable stability only during the first 2 weeks. Dowex MAC-3<sup>®</sup> peracid resin lost 50% of its oxidation capacity after two weeks of storage on the bench.



**Graph 2. 33** Oxidation capacity of the three samples of peracid resin **2.18c** over 7 weeks

Another method used in the analysis of the oxidation capacity of the peracid resins was the differential scanning calorimetry (DSC),<sup>116</sup> a technique used to measure the heat ( $\Delta H_d$ ) of decomposition of the percarboxylic acid groups.



**Figure 2. 12** Differential Scanning Calorimetry (DSC) thermogram of peracid resin **2.18c**

The thermogram obtained from a sample of Dowex MAC-3<sup>®</sup> peracid resin **2.18c** shows that the decomposition of the peracid groups is an exothermic reaction (Figure 2.12). From the correlation between ( $\Delta H_d$ ) and the oxidation capacity measured by iodometry, it was found that for Dowex MAC-3<sup>®</sup> peracid resin **2.18c** 44.5 cal of energy were evolved per mequiv of peracid group decomposed by heating (Equation 2.1). This value can be used to determine the oxidation capacity of Dowex MAC-3<sup>®</sup> peracid resin by DSC analysis using the following formula.

$$\Delta H_d \text{ per unit of peracid group} = \frac{\Delta H_d = -1270.99 \text{ J/g} = 303.77 \text{ cal/g}}{\text{Iodometric Titration} = 6.8 \pm 0.7 \text{ meq/g (10\% error)}}$$

**Equation 2. 1** Oxidation capacity determined by the ratio between  $\Delta H_d$  and the value obtained by iodometric titration

The advantage of DSC over the titration was that less time and smaller quantities of compound were required. In fact, analysis via iodometric titration required 700-900 mg of resin, while it is possible carry on a DSC analysis with 2 mg of resin. The data

obtained by DSC were useful to classify the reactivity of the supported reagent.<sup>117</sup> The energy released during a reaction is a measure of the stored potential chemical energy ( $\Delta H_d$ ). The temperature at which a system exhibits significant exothermic activity is called the onset temperature ( $T_O$ ), which related to the rate of a chemical reaction large enough to be measured by the calorimeter. The onset temperature is thus a measure of the reaction kinetics.

The values of ( $\Delta H_d$ ) and ( $T_O$ ) can be used to classify reactive chemicals into four hazard classes:

- Class I – Low T and High  $\Delta H$ : compounds that react at low temperatures, liberating a large amount of heat.
- Class II – High T and High  $\Delta H$ : compounds that react releasing a significant heat at high temperature.
- Class III – Low T and Low  $\Delta H$ : compounds that react at low temperatures, similar to compounds of Class I, but with less exothermic decompositions.
- Class IV – High T and Low  $\Delta H$ : compounds that react at higher temperatures and give mildly exothermic decompositions.

Thus, reactive hazards decrease from Class I to IV. The calorimetric data of Dowex MAC-3<sup>®</sup> peracid resin are listed in Table 2.3, and compared with the data of other compounds. The compounds are assigned to the four reactive classes based on the values of ( $\Delta H_d$ ) and ( $T_O$ ), as illustrated in Figure 2.13.

Table 2. 3 DSC data for various compounds

Entry	Compound	T (°C)	- $\Delta H$ (Kcal/g)
1	<i>p</i> -Nitrotoluene	366	0.37
2	3,5-Dinitrobenzoic acid	374	0.76
3	Trinitrotoluene	314	1.29
4	Benzoyl peroxide	108	0.44
5	<i>t</i> -Butyl hydroperoxide	98	0.25



6	Cumene hydroperoxide	187	0.45
7	Benzyl chloride	172	0.27
8	2-Bromo- <i>n</i> -butyric acid	91	0.31
<u>9</u>	<u>Dowex MAC-3<sup>®</sup> Peracid resin</u>	<u>145</u>	<u>0.30</u>

The chemicals in Class I are more likely to decompose violently and should be carefully handled and thoroughly tested. Chemicals in Class II also lie in the high-hazard category since they release large amounts of energy. Substances in Class III and IV pose medium and low risk, respectively.

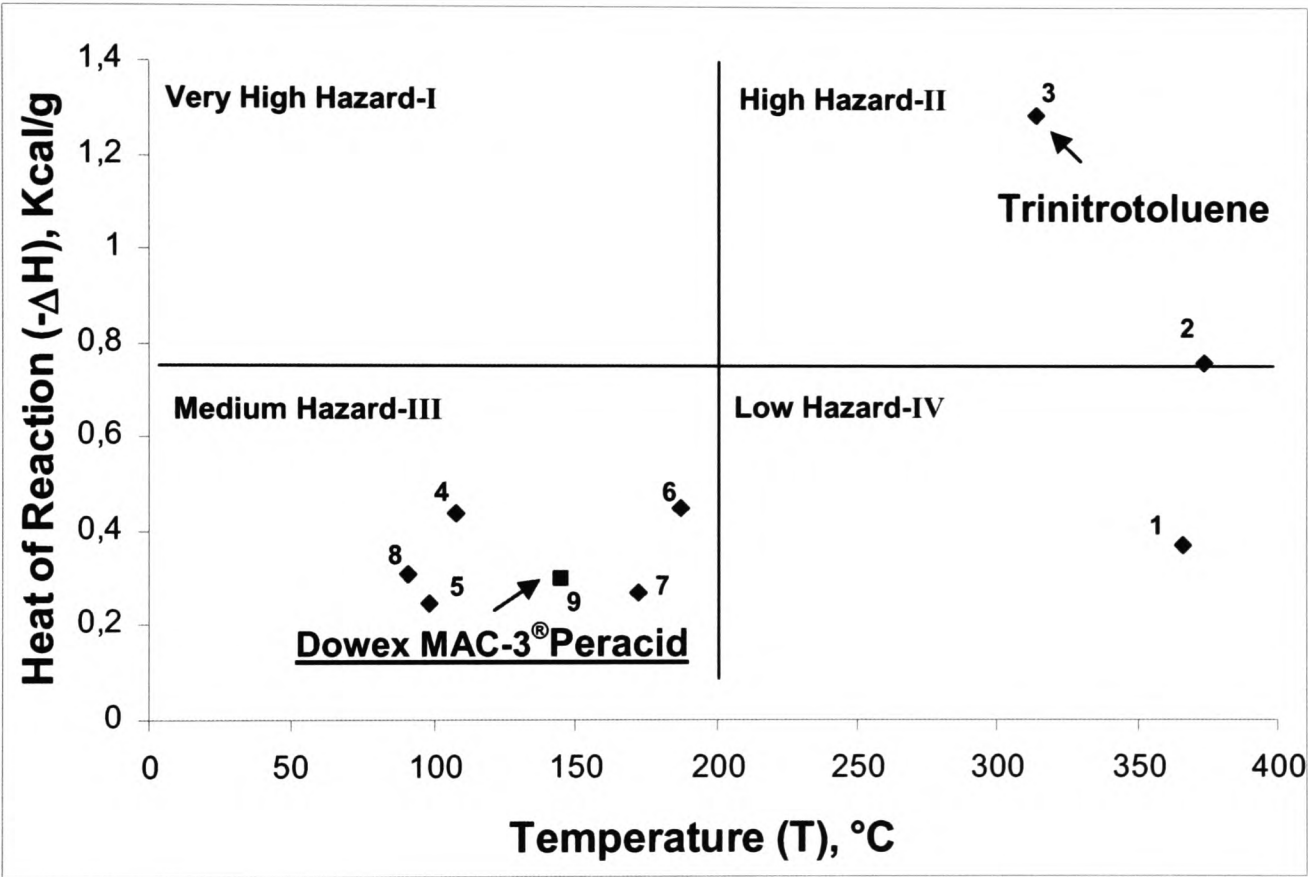


Figure 2. 13 Calorimetric data for the compounds in Table 2.2

Dowex MAC-3<sup>®</sup> peracid resin **2.18c** lies in Class III showing reactivity comparable to others peroxides (entries 4, 5), but can be used safely in normal laboratory practice.

## 2. 6 Conclusions

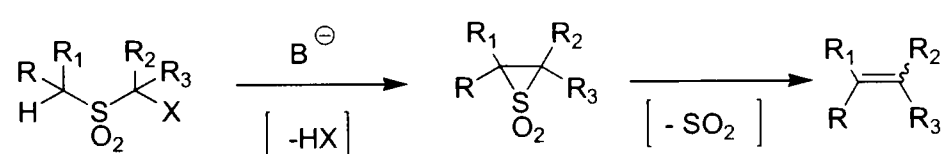
Generally macroporous resins required more drastic reaction conditions to be functionalised, because of a lower swellable capacity which makes poor availability of the reactive groups. This explains why, in the preparation of a supported macroporous peracid, increasing the temperature, the concentration of  $\text{H}_2\text{O}_2$  and the reaction gave several benefits. Furthermore, an increase in temperature causes rapid decomposition of  $\text{H}_2\text{O}_2$  which makes  $\text{O}_2$  available for the oxidation of the carboxylic acid resins to peracid ones. The values for Amberlite IRP-64<sup>®</sup> peracid resin **2.18a** are worsen by the size of the beads, which make washing and filtering the resin more difficult. For Amberlite IRC-50<sup>®</sup> peracid resin **2.18b** a value of 1.3 mequiv/g represents a good result when compared to data reported in the literature. Dowex MAC-3<sup>®</sup> peracid resin **2.18c** showed the best oxidation capacity of 6.7 mequiv/g, this result was obtained using 8 equiv of 50 wt. %  $\text{H}_2\text{O}_2$  at 50 °C for 16 h.

### 3. Applications of polymer-supported peracids

#### 3. 1 Chemoselective oxidation of sulfides to sulfones

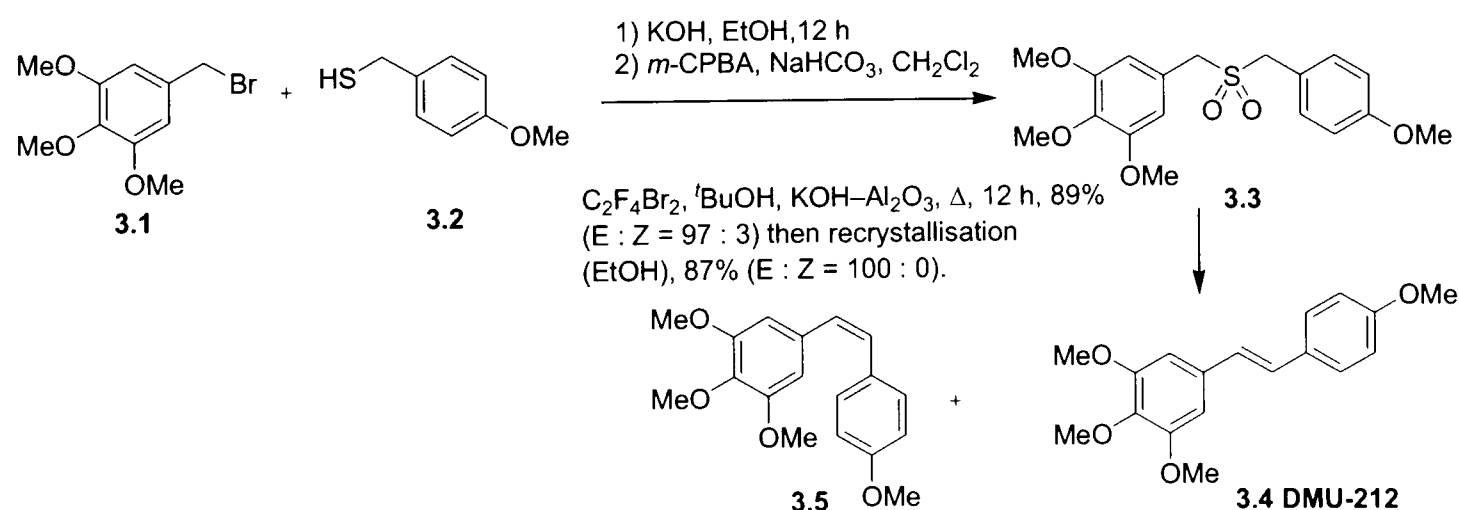
##### 3.1. 1 General overview

Organosulfur compounds<sup>118-120</sup> are important reagents in organic synthesis and they are useful for the preparation of biologically and medically important products. The sulfonyl group is often used to allow the construction of carbon-carbon bonds via carbanion-stabilised rearrangements and eliminations. An important application, for example is the Ramberg-Bäcklund reaction,<sup>121</sup> which converts an  $\alpha$ -halo sulfone into an alkene in the presence of a base with elimination of sulphur dioxide (Scheme 3.1).



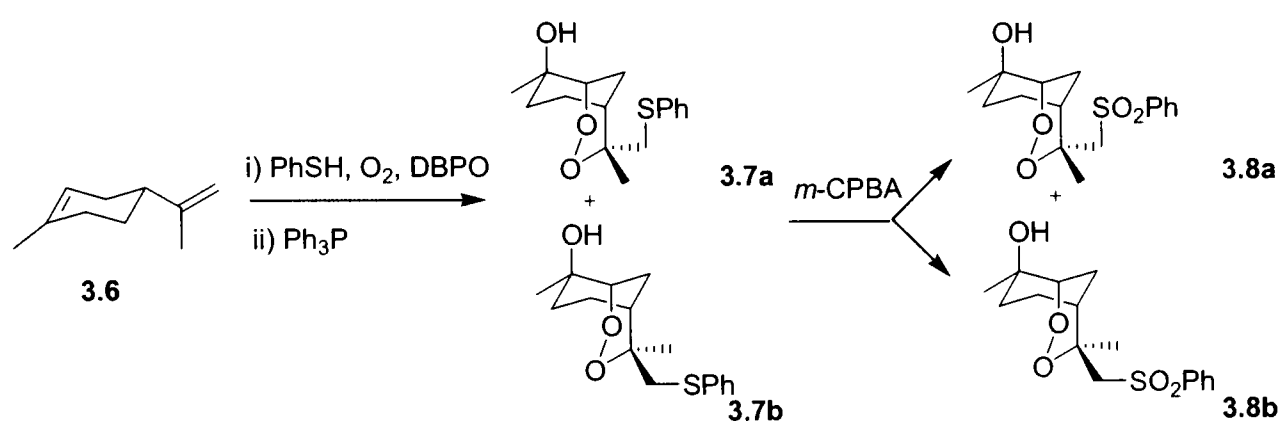
**Scheme 3.1** The Ramberg-Bäcklund reaction [ X = Cl, Br etc.; B = base]

The Ramberg–Backlund reaction has been used, for example, to prepare (E)-stilbene **3.4**, known as DMU-212,<sup>122</sup> which is a potent anticancer agent. Sulfone **3.3** was prepared by coupling of bromide **3.1** with thiol **3.2** followed by oxidation of the resultant sulfide with *m*-CPBA, the reaction of sulfone **3.3** proceeded with high selectivity in 89% yield and a (E) : (Z) ratio of 97 : 3 (Scheme 3.2).



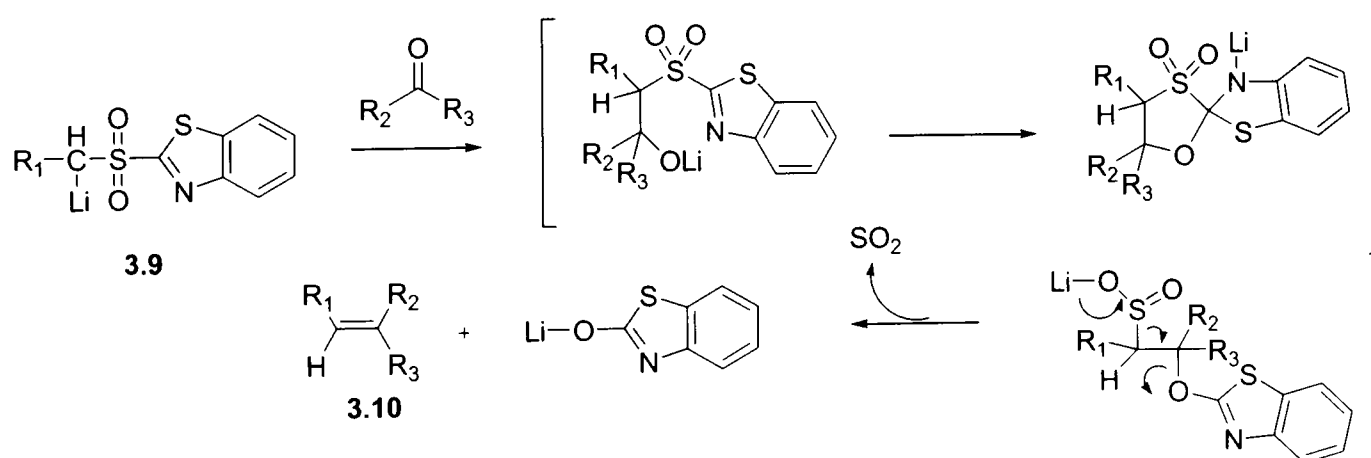
**Scheme 3.2** Synthesis of anti-cancer agent DMU-212

Sulfones have also found applications in the discovery of new antimalarial agents.<sup>123, 124</sup> Endoperoxide sulfones **3.8a, b** derived from *R*-(+)-limonene **3.6** were obtained in a one pot process which involves thiol oxygen cooxidation of the terpene, followed by selective reduction of the resulting endoperoxide-hydroperoxide (Scheme 3.3). Oxidation of sulfide **3.7a, b** with *m*-CPBA followed by chromatography afforded sulfones **3.8a** and **3.8b**. These compounds exhibit higher antimalarial activity compare to their sulfide analogs.



**Scheme 3.3** Synthesis of sulfone derivatives as potent antimalarial agent

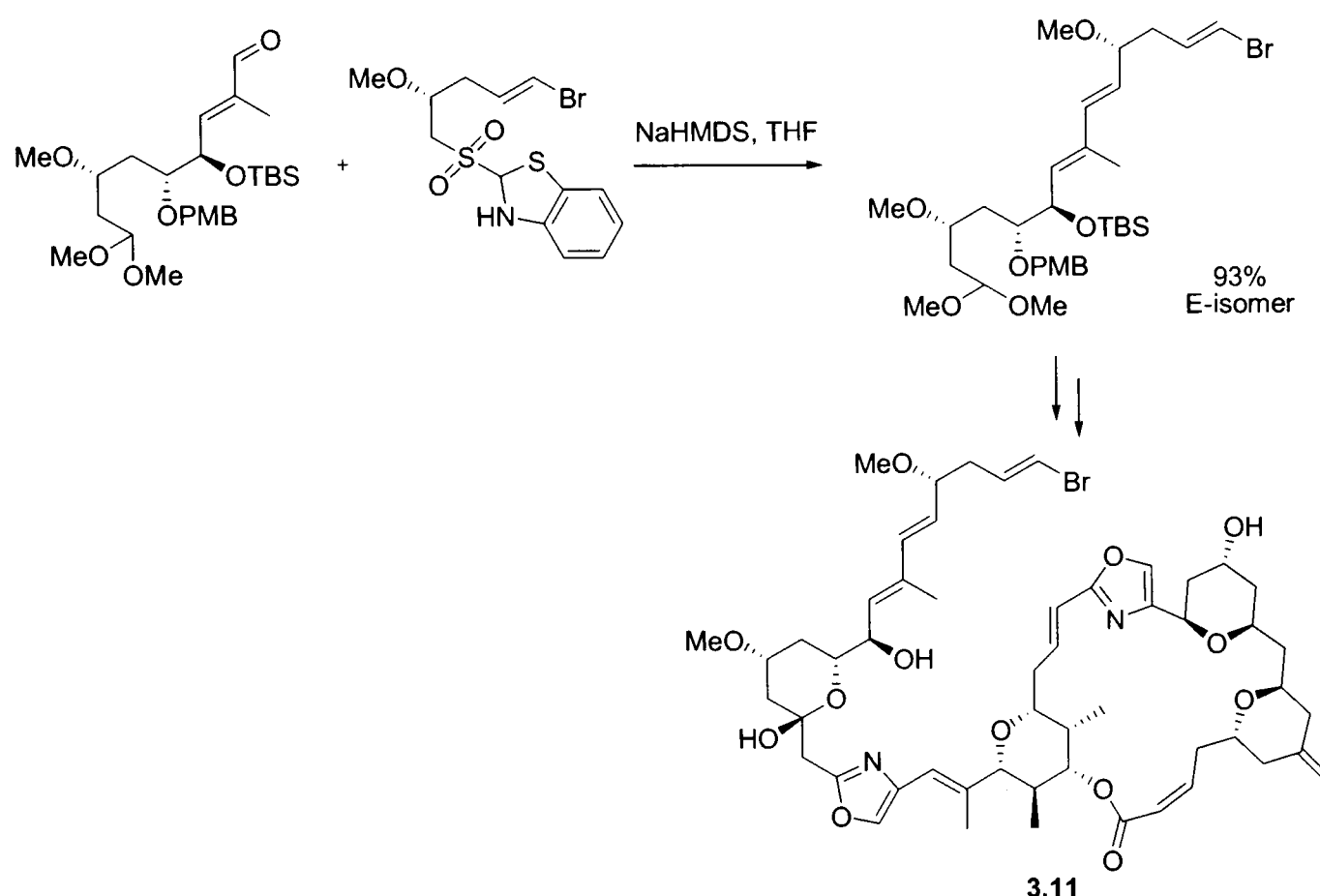
Sulfones have also been successfully employed in Julia–Kocienski olefination of carbonyl compounds.<sup>125-127</sup> Benzothiazole-sulfones **3.9** are easily prepared by oxidation of the corresponding sulfides with potassium permanganate or by hydrogen peroxide. When treated with lithium diisopropylamide (LDA) the sulfones give the corresponding  $\alpha$ -lithio derivatives **3.9** which after reaction with ketones/aldehydes afford the olefins **3.10**.



**Scheme 3.4** Mechanism of Julia–Kocienski's olefination



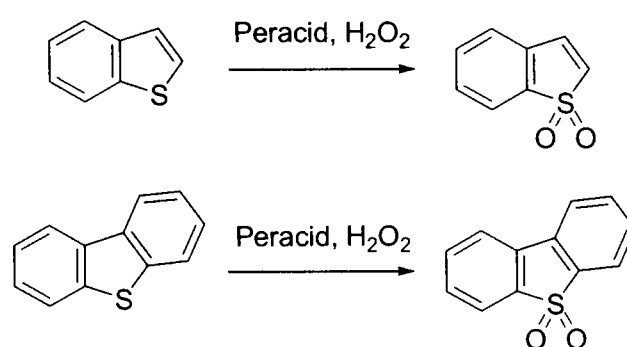
Since the initial study by Julia and Kocienski of the reaction of benzothiazole-sulfones **3.9** with carbonyl compounds, the versatility of these sulfone derivatives has been demonstrated through their application in total synthesis of a large number of biologically active natural products such as (+)-lasonolide A,<sup>128</sup> phorboxazole A **3.11**,<sup>129</sup> and (-)-elisapterosin B.<sup>130</sup>



**Scheme 3.5** Synthesis of (+)-phorboxazole A using a Julia–Kocienski's olefination

The synthesis of sulfones is an important process also in the context of desulfurisation of fuels. The purpose of removing the sulfur is to reduce the sulfur dioxide emissions, that result from using fuels. In fact, sulfur, even in extremely low concentrations, can poison the precious metal catalyst used in the refining of gaseous effluents. In the petroleum refining industry, catalytic hydrodesulfurisation is currently used for reducing the sulfur content of the liquid products. However organic sulfides: thiophenes, benzothiophenes, and dibenzothiophenes, that are the major sulfur-containing compounds present in liquid hydrocarbon fuels, are refractory to the hydrodesulfurisation. Alternative processes have been employed, for

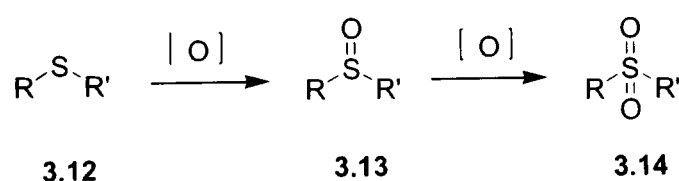
instance physical extractions with a liquid, selective adsorptions on suitable materials, reductive and oxidative microbial processes, or catalytic oxidations. In the latter case, various types of oxidants are used, including nitrogen oxides, nitric acid, ozone, *t*-butylhydroperoxide, oxygen, air and peracids. In particular, peracids have been used in combination with aqueous solutions of hydrogen peroxide (Scheme 3.6). The oxidised organic sulfur compounds transfer into the water phase, and are removed by a simple liquid–liquid separation.



**Scheme 3. 6** Oxidation of aromatic sulfur compounds in fuels by hydrogen peroxide and peracid

### 3.1. 2 Reagents for chemoselective oxidation of sulfides to sulfones

The use of sulfones in organic synthesis has continued to grow over the years,<sup>131, 132</sup> thus, a considerable number of studies have been made to search for a system able to carry out oxidation of sulfides fast and efficiently. Many oxidising systems have been successfully applied to the oxidation of sulfides to sulfoxides, however little work has been done on the chemoselective oxidation of sulfides to sulfones. The oxidation of sulfide normally proceeds in two steps involving first the formation of sulfoxide **3.13** and subsequently its transformation to the sulfone **3.14** (Scheme 3.7). The sulfoxide intermediate **3.13**, could not be completely consumed in the oxidation process and found as a contaminant.<sup>133</sup>



**Scheme 3.7** General mechanism for the oxidation of sulfides to sulfone

In the literature, there are a number of available methods to carry out selective oxidations of sulfides to sulfones (Table 3.1).

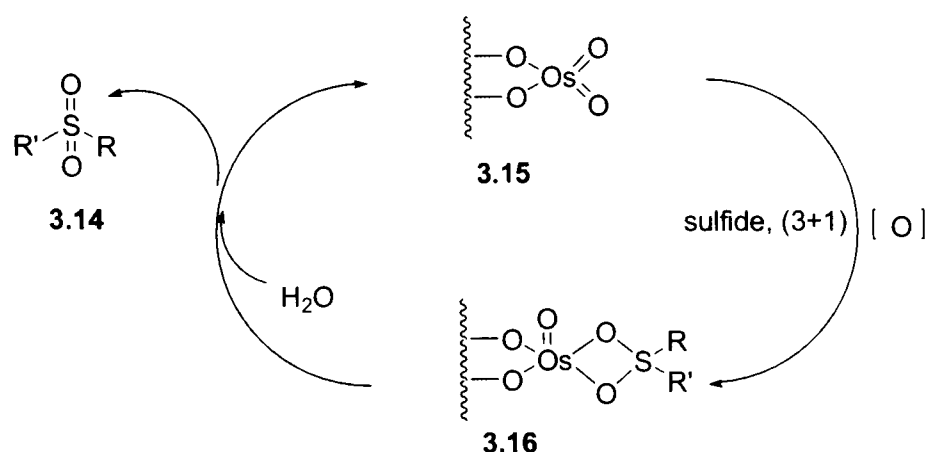
**Table 3.1** Common reagents for the selective oxidation of sulfides to sulfones

$$\begin{array}{ccc} \text{R}-\text{S}-\text{R}' & \longrightarrow & \begin{array}{c} \text{O} \\ \parallel \\ \text{R}-\text{S}-\text{R}' \\ \parallel \\ \text{O} \end{array} \\ \text{3.12} & & \text{3.14} \end{array}$$

Entry	Method
1	H <sub>2</sub> O <sub>2</sub> in AcOH <sup>134, 135</sup>
2	H <sub>2</sub> O <sub>2</sub> /Catalyst <sup>136-138</sup>
3	TBHP <sup>139, 140</sup>
4	HNO <sub>3</sub> / <i>m</i> -CPBA <sup>141</sup>
5	KMnO <sub>4</sub> <sup>142</sup> /MnO <sub>2</sub> <sup>143</sup>
6	RuO <sub>4</sub> <sup>144</sup>
7	OsO <sub>4</sub> -NMO <sup>145</sup>
8	CrO <sub>3</sub> /H <sub>5</sub> IO <sub>6</sub> <sup>146</sup>

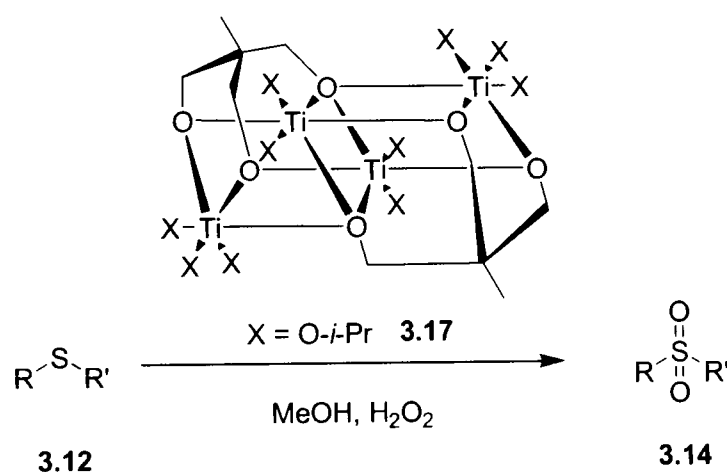
Unfortunately, most of these reagents do not give satisfactory results for medium-scale synthesis, because of the low oxidising oxygen content and high cost of the metal catalysts. In addition when a metal catalyst is employed, it is necessary to consider also other factors such as: toxicity of the transition metal, recovery of the catalyst, removal of the metal from the final product. Recyclable heterogeneous oxidations are preferred over homogeneous analogues, synthetic procedures are simplified and automation is possible. Choudary<sup>147</sup> for example described the direct oxidation of sulfides to sulfones using molecular oxygen as the stoichiometric oxidant and osmate exchanged layered double hydroxide as a recyclable catalyst. The mechanism involves a concerted [3+1] cycloaddition *via* the delivery of two oxygens (Scheme 3.8).





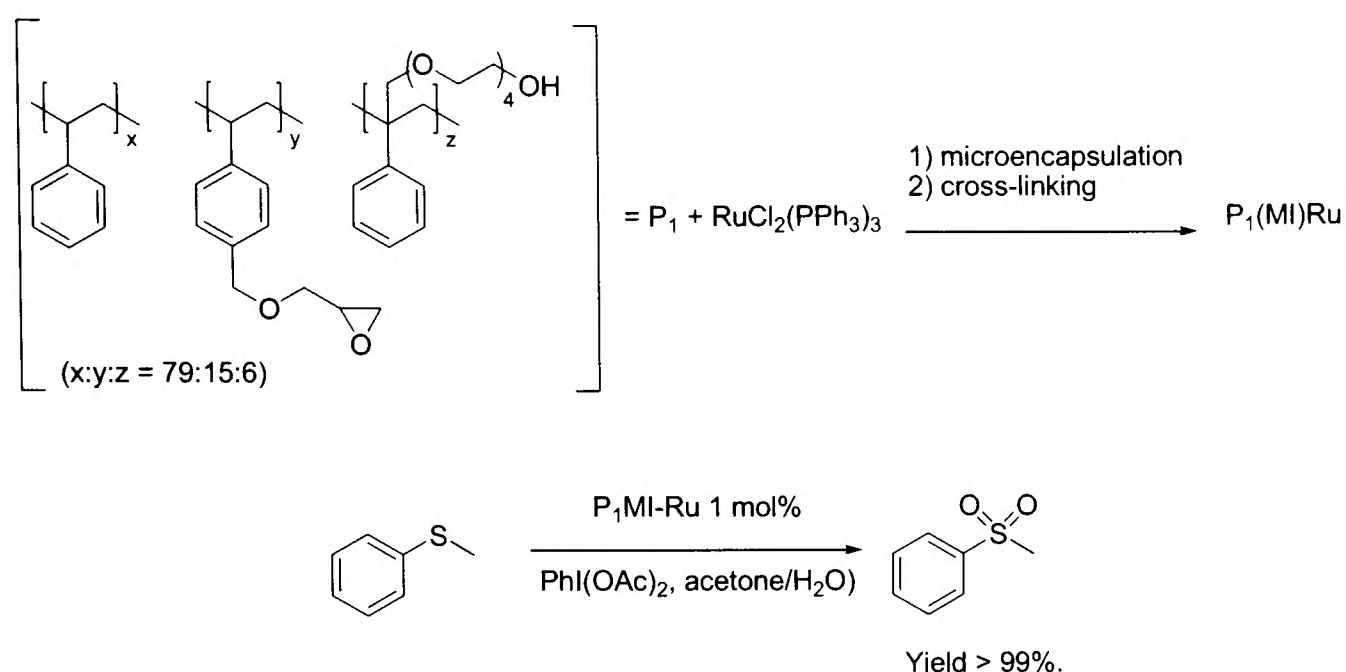
**Scheme 3.8** Postulated mechanism for the oxidation of sulfides using osmate exchanged layered double hydroxide and  $\text{O}_2$

Titanium complex<sup>148</sup> **3.17** have been also successfully employed for selective conversion of sulfides to sulfones. Room temperature ionic liquids were employed to immobilise the catalyst, thus, allowing the catalyst to be recycled several times (Scheme 3.9).



**Scheme 3.9** Tetrameric titanium alkoxide/ionic liquid for selective oxidation of sulfides to sulfones

Recently a ruthenium catalyst was also immobilised using a polymer–micelle incarcerated method.<sup>149</sup> The oxidation was carried out in the presence of iodobenzene diacetate to afford selectively the sulfone (Scheme 3.10). The catalyst could be recovered and reused several times without loss of activity and metal leaching was not observed.

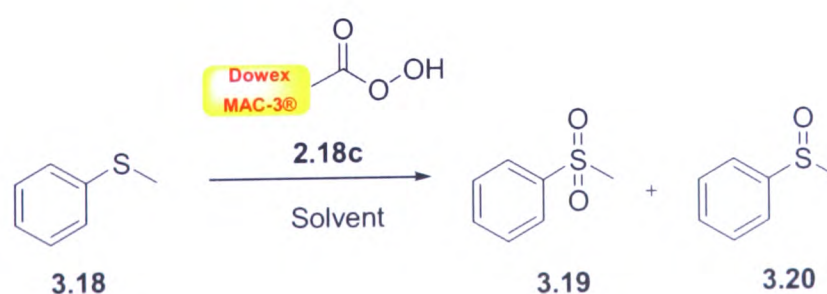


**Scheme 3.10** Synthesis of sulfone using a polymer micelle incarcerated ruthenium catalyst

### 3.1. 3 Chemoselective oxidation of sulfides to sulfones using polymer-supported peracids

In the course of the previous investigations described in chapter II, a procedure that allowed the oxidation of Dowex MAC-3<sup>®</sup> to a stable and high loading percarboxylic resin **2.18c** was developed. The use of this novel supported peracid in the selective oxidation of sulfides to the corresponding sulfones was explored. Initial studies were focused on the oxidation of thioanisole to its corresponding sulfone, and the influence of solvents on the oxidation properties of the resin was investigated. It was found that Dowex MAC-3<sup>®</sup> peracid resin **2.18c** showed high efficiency and selectivity with only the corresponding sulfone obtained, when a 5 fold excess of reagent was used.

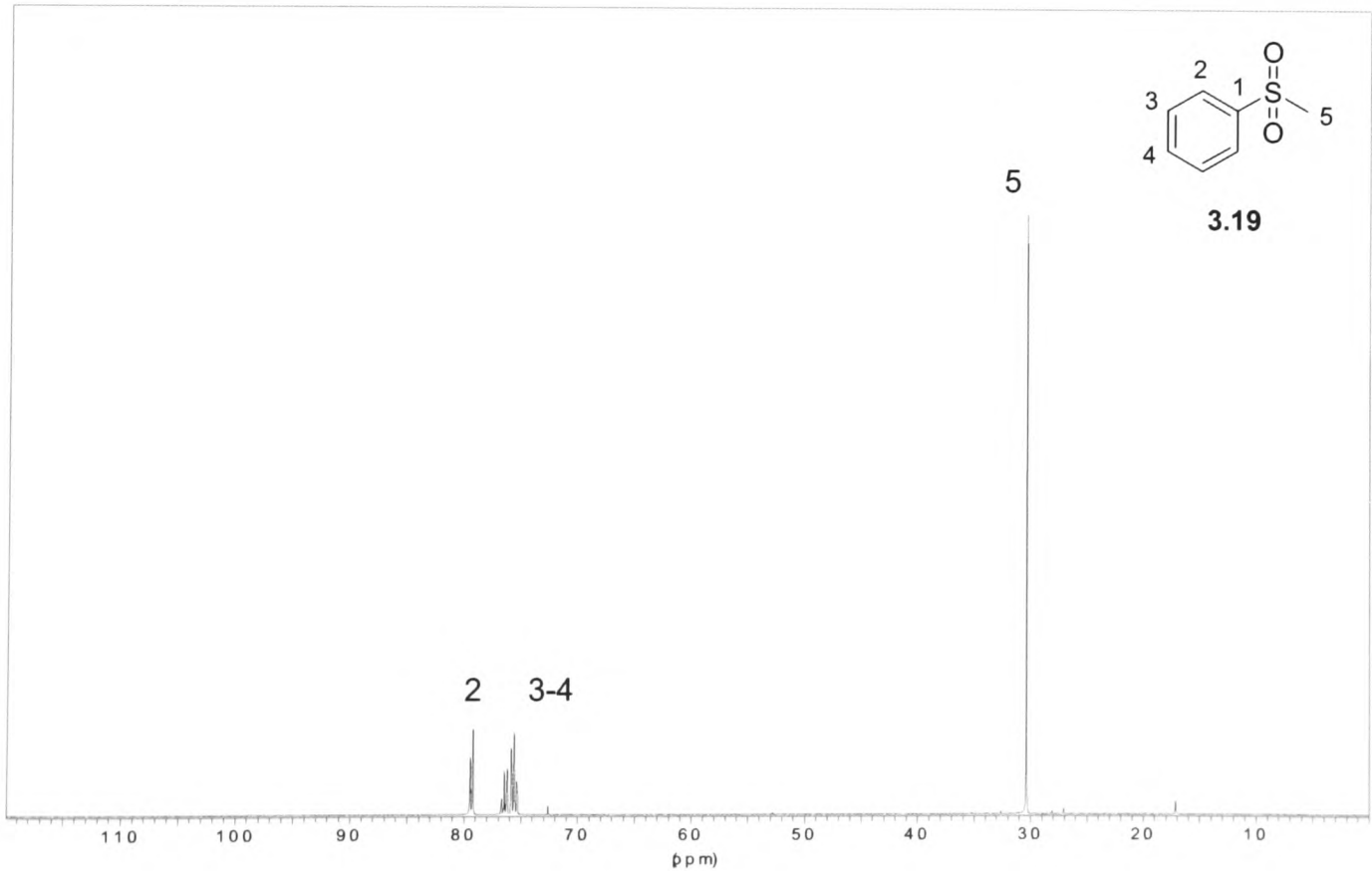
**Table 3.2** Evaluation of the optimal solvent for the oxidation of thioanisole



Entry	Solvent	Time	Conversion <sup>a</sup> (%)	Yield <sup>b</sup> (%)	
				3.19	3.20
1	MeOH	0.75 h	100	> 98	-
2	Dioxane	3 h	100	> 98	-
3	CH <sub>3</sub> CN	1 h	100	> 98	-
4	DCM	6 d	95	86	4
5	DMF	0.5 h	100	> 98	-
6	THF	0.25 h	100	> 98	-

<sup>a</sup>Conversion by HPLC. <sup>b</sup>Determined by <sup>1</sup>H-NMR spectroscopy.

The reaction was monitored by HPLC, when all the sulfide was consumed, the resin was filtered off and the product isolated by evaporation.<sup>150</sup> When THF was used as a solvent, sulfone **3.19** was isolated in quantitative yield and high purity after just 15 min (Figure 3.1).

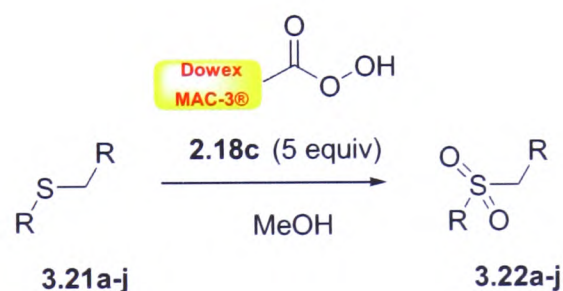


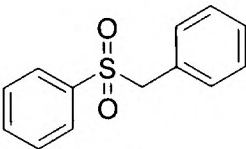
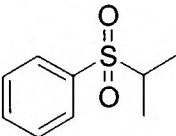
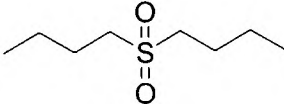
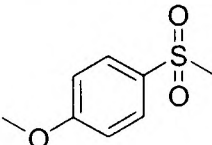
**Figure 3. 1** <sup>1</sup>H-NMR (CDCl<sub>3</sub>) of crude methyl phenyl sulfone **3.19** synthesised using resin **2.18c**

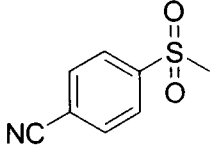
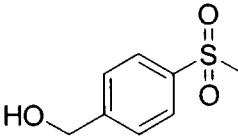
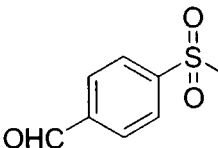
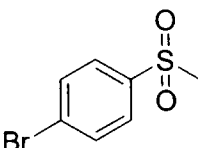
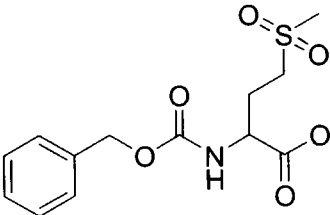
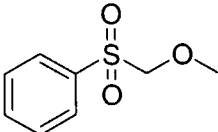


Due to the high rate of oxidation, the presence of peroxides in THF was checked using the well known potassium iodide test, which shown to be positive. THF is of course a peroxide-forming solvent, with explosive implications, and for this reason another solvent (methanol) was chosen to perform the oxidations. However from the results in Table 3.2, it is clear that DMF was also a good solvent for an efficient and rapid transformation. Using these optimised conditions, the oxidation of aryl-alkyl sulfides was attempted. The results are summarised in Table 3.3. In all cases, high chemoselectivity toward formation of sulfones was observed, with all the substrates completely converted and products recovered in high yield and purity after resin removal and solvent evaporation.

**Table 3.3** Selective sulfide oxidation to sulfone using Dowex MAC-3<sup>®</sup> peracid resin **2.18c**



Entry	Product	Time (h)	Yield <sup>a</sup> (%)
1	 <b>3.22a</b>	2.5	>98
2	 <b>3.22b</b>	1.5	>98
3	 <b>3.22c</b>	3	>98
4	 <b>3.22d</b>	3.5	>98

5	 3.22e	3.5	>98
6	 3.22f	1.5	>98
7	 3.22g	6	>98
8	 3.22h	3	>98
9	 3.22i	6	>98
10	 3.22j	1.5	>98

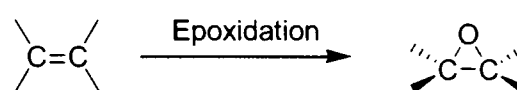
<sup>a</sup>Determined by <sup>1</sup>H-NMR spectroscopy.

Peracid resin **2.18c** worked efficiently with a range of substrates both electron rich and poor. Moreover with bulky substrates (Table 3.3, entries 1, 2, 3) good yields and rates were also observed.

## 3. 2 Oxidation of alkenes

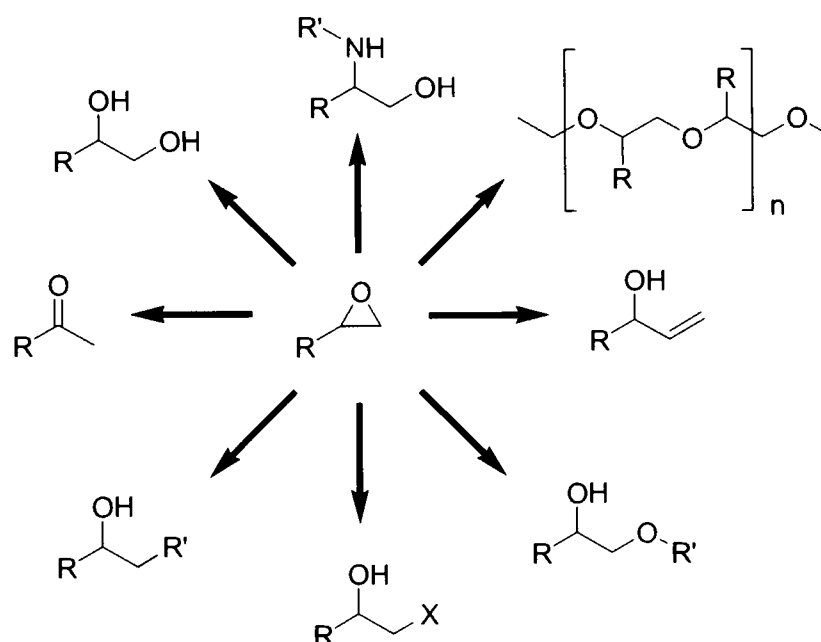
### 3.2. 1 Introduction

Alkenes are found in great abundance in organic molecules, and undergo a most useful transformation known as epoxidation. Two new possible stereogenic carbon are generated from a prochiral carbon-carbon double bond (Scheme 3.11).<sup>151</sup>



**Scheme 3.11** Representation of the epoxidation of an alkene

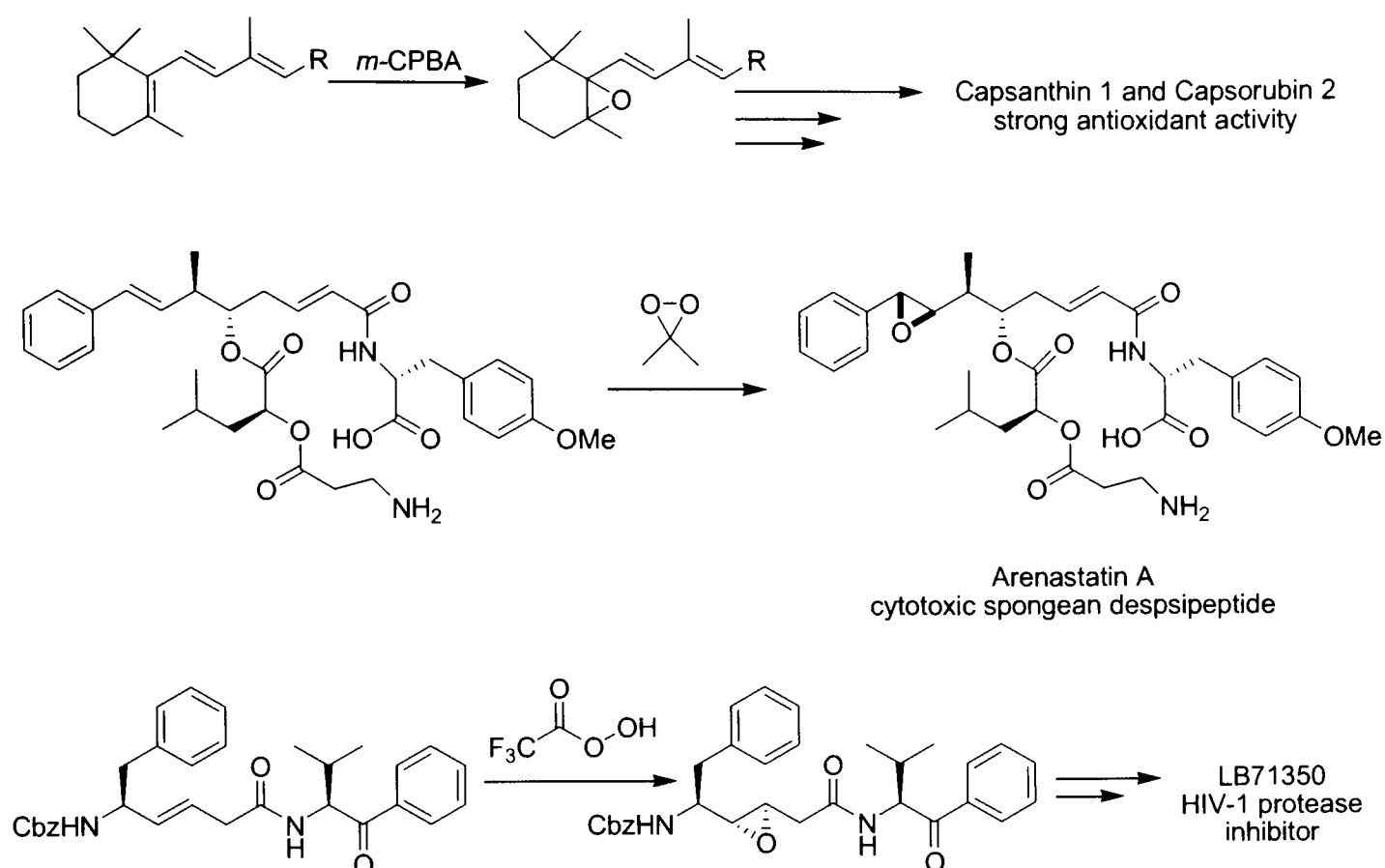
Epoxides are activated towards nucleophilic attack, which makes them useful and versatile intermediates in organic chemistry for the synthesis of a range of important commercial products.<sup>152</sup> For example reductions, rearrangements or ring-opening reactions with various nucleophiles give diols, aminoalcohols, allylic alcohols, ketones, polyethers etc. as depicted in Scheme 3.12.



**Scheme 3.12** Versatility of epoxides (R = alkyl, aryl)

The wide number of applications of epoxides has meant that they have played a fundamental role in the synthesis of natural compounds,<sup>153</sup> pharmaceuticals,<sup>154</sup> food additives<sup>155</sup> and pesticides (Scheme 3.13). In



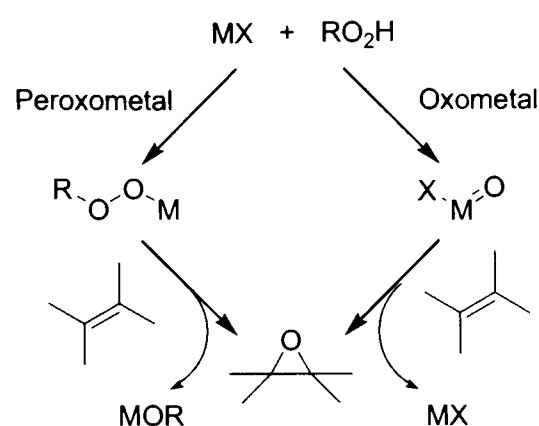


Scheme 3.13 Examples of epoxides in organic synthesis

A massive number of possible oxidants were largely presented in literature,<sup>156-158</sup> but all of them can be covered in two main categories: metal catalysed epoxidations and organocatalysed epoxidations.

### 3.2. 2 Metal catalysed epoxidations

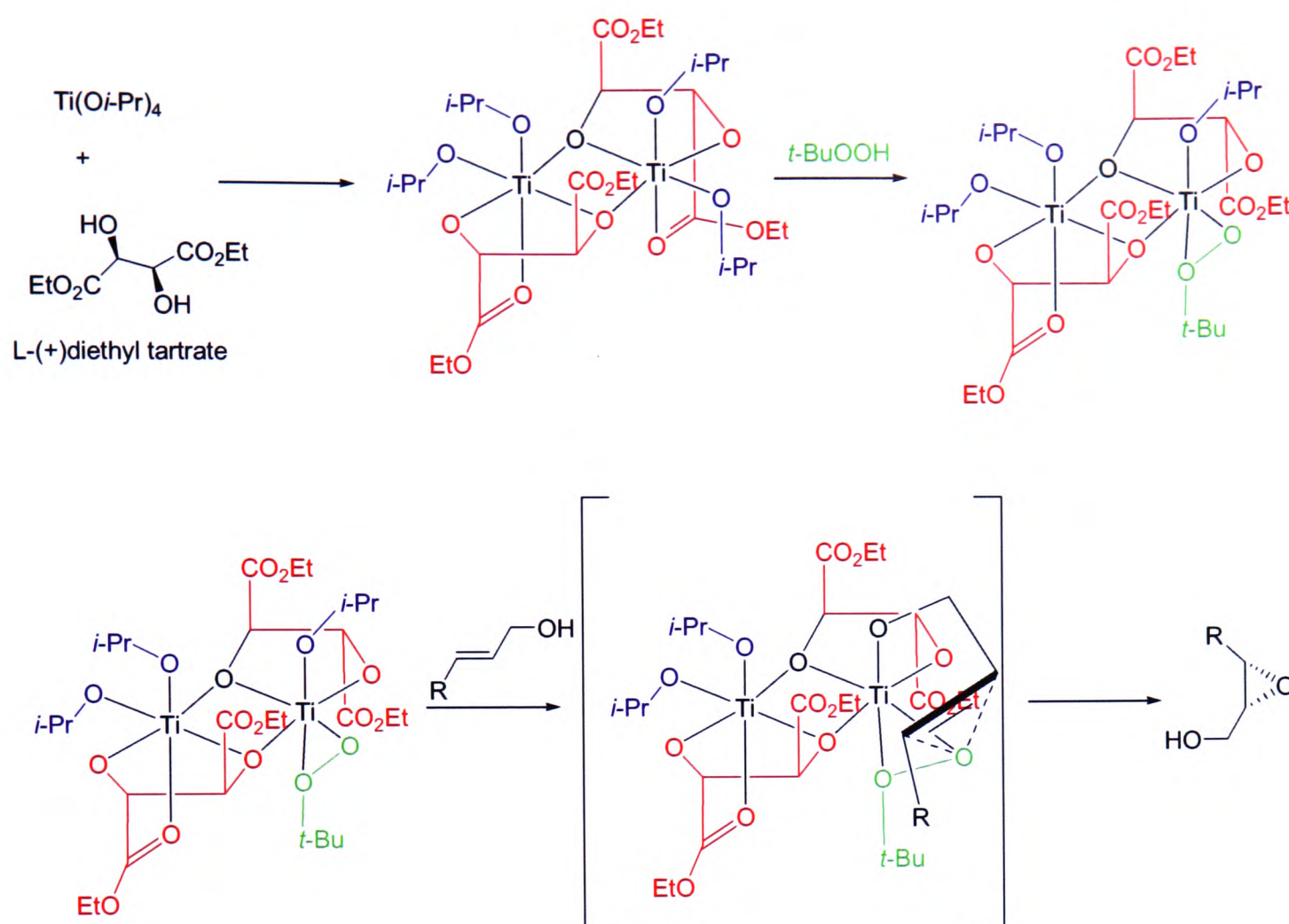
Metal-catalysed epoxidations can be divided into two categories on the basis of the key intermediate involved in the oxygen-transfer step.<sup>159</sup> The first one involves a peroxometal pathway, while the second one involves an oxometal pathway. Molybdenum, vanadium and titanium catalysed epoxidations are believed to proceed via a peroxometal pathway.<sup>160</sup> Oxometal species, on the other hand, are generally accepted as reactive intermediates in catalytic epoxidations with ruthenium, osmium and chromium (Scheme 3.14). The two most famous examples of these two categories are respectively: the Sharpless epoxidation for the peroxometal pathway and the Jacobsen-Katsuki epoxidation *via* the oxometal pathway.



**Scheme 3.14** Peroxometal versus oxometal pathways in catalytic epoxidation reactions

### 3.2. 3 Sharpless epoxidation

This method, developed in 1980 by Sharpless's research group has proven to be useful for the conversion of allylic alcohols into almost pure enantiomers of epoxides using *tert*-butyl hydroperoxide as the oxidant, titanium (IV) isopropoxide as a catalyst, and either (*R,R*) or (*S,S*)-diethyl or diisopropyl tartrate as a chiral ligand.<sup>161</sup> The catalyst is prepared *in situ* from titanium-*iso*-propoxide and enantiomerically pure tartaric acid diethyl ester. Using 5-10 mol% of the titanium alkoxide and 10-20 mol% excess of the tartrate with respect to titanium-*iso*-propoxide, high enantioselectivities (>90%) and yields (>80%) are obtained for a range of substituted allylic alcohols. The hydroxyl moiety of the substrate has an activating and stereodirecting role *via* binding to the metal centre, and provides high enantioselectivities in the epoxidation reaction. From spectroscopic data it was concluded that the titanium complex exists as a dimer in solution (Scheme 3.15).

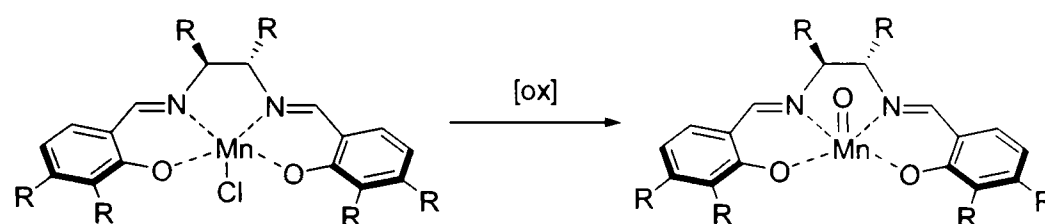


Scheme 3.15 Sharpless epoxidation of allylic alcohols

Different allylic alcohols coordinate to the titanium- $\text{L-(+)-diethyl tartrate}$  complex offering the same enantiotopic face to the bound oxidizing agent.  $\text{L-(+)-tartrate}$  is ideal as a chiral ligand because it is readily available and relatively inexpensive (although  $\text{D-(-)-tartrate}$  is more expensive).

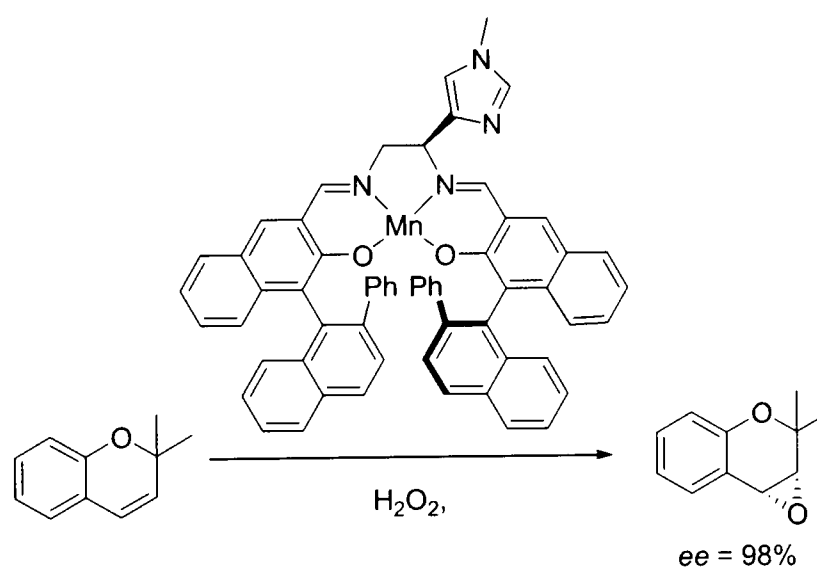
### 3.2. 4 Jacobsen-Katsuki epoxidation

In the 1990s, Jacobsen's and Katsuki's research groups independently developed methods for enantioselective epoxidation of alkenes without allylic OH groups. The Jacobsen-Katsuki reaction requires bleach or hydrogen peroxide as an oxidant and a chiral  $\text{Mn(III)}$  complex, to direct oxygen delivery to the alkenes. The oxidising species in the catalytic oxidation reaction is proposed to be a  $\text{Mn}^{\text{V}}$ -oxo intermediate (Scheme 3.16).



**Scheme 3.16** The original Jacobsen-Katsuki catalyst

The Mn-salen catalyst gave generally an *ee* up to 90% with yields exceeding 80% when used with *cis*-alkenes. In contrast the epoxidation of *trans*-olefins showed moderate selectivities (*ee* < 60%), however, these results could be improved by the introduction of additional chiral groups at the 3'-position of the phenolate ring of the ligand. The stability of the Mn-salen complexes is often a severe problem and turnover numbers are usually found in the range of 40-200. Recently, an extremely robust salen catalyst was reported by Katsuki, based on a ligand which possesses an internal pyridine or *N*-methylimidazole ligand attached to the diamine bridge. With this new catalyst 2,2-dimethylchromene was converted to the corresponding epoxide in 98% *ee* (Scheme 3.17).<sup>162</sup>



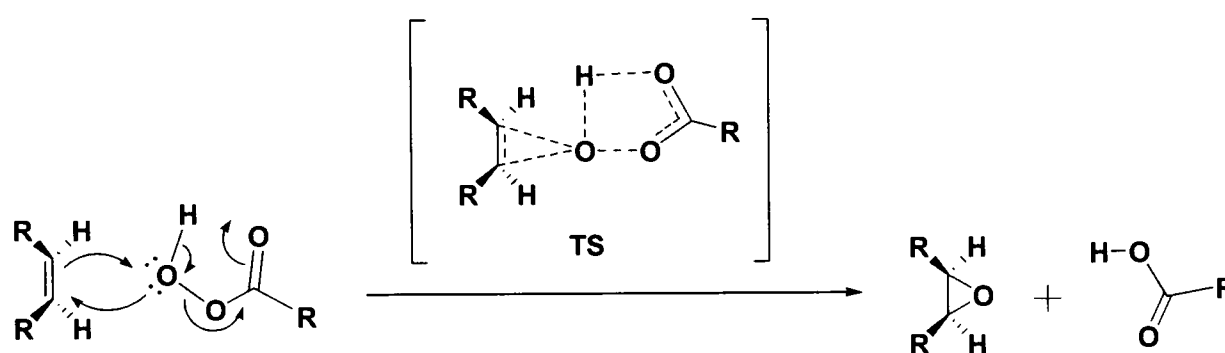
**Scheme 3. 17** Asymmetric epoxidation of 2,2-dimethylchromene catalysed by manganese complex

### 3.2. 5 Organocatalysed epoxidations

Examples of organocatalysed epoxidation reagents include: dioxiranes, alkylhydroperoxides, hydrogen peroxide, hypochlorite, iodosylbenzene and oxygen.



Peroxydicarboxylic acids as peroxyacetic acid, *m*-chloroperoxybenzoic<sup>163</sup> and peroxytrifluoroacetic acid are widely used stoichiometric reagents for epoxidation in industrial and academic research (e.g. Prilezhaev reaction).<sup>164</sup> Classically, the concerted mechanism originally proposed by Bartlett<sup>165</sup> suggests a symmetrical transfer of an oxygen atom to the olefin from the internally hydrogen bonded peracid monomer, through a transition state with a "butterfly" configuration (Scheme 3.18). Bartlett's cyclic planar concerted mechanism is reasonable in view of experimental observations: (1) the reaction has a second order kinetic, (2) the reaction occurs readily even in non polar solvents, (3) the oxygen addition is stereospecific, (4) the reaction is insensitive to steric effects.



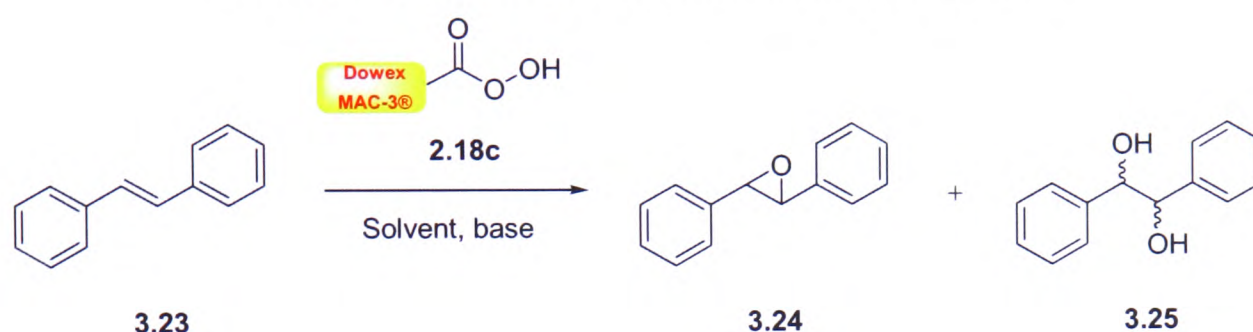
**Scheme 3.18** Bartlett's mechanism for epoxidation by percarboxylic acids

### 3.2. 6 Oxidation of alkenes by Dowex MAC-3<sup>®</sup> peracid resin

The employment of peracid resins for direct epoxidation of alkenes has been reported,<sup>88-90, 96, 97</sup> but the oxidations are often carried out only in environmentally unfriendly chlorinated solvents. Dowex MAC-3<sup>®</sup> peracid resin **2.18c** allowed screening of various solvents in the oxidation of *trans*-stilbene as a model substrate. The influence of solvent and amount of Dowex MAC-3<sup>®</sup> peracid resin **2.18c** was also investigated. Representative results are shown in Table 3.4. After a series of experiments, acetonitrile demonstrated good compatibility with the resin, being able to dissolve the substrates, as well as offering the best results in terms of selectivity and reaction time (Table 3.4, entries 6,7). However, the presence of mild inorganic bases, such as potassium carbonate, were necessary to avoid side reactions; such as the formation of diols from the corresponding epoxides (oxidations were monitored

by HPLC, with the identity of products determined by comparison with commercial samples using  $^1\text{H-NMR}$  analysis). A series of experiments on the effects of the temperature were carried out using conventional and microwave heating. It was observed that a temperature greater than 40 °C lead to rapid decomposition of the resin.

**Table 3. 4** Oxidation of *trans*-stilbene **3.23** by resin **2.18c**

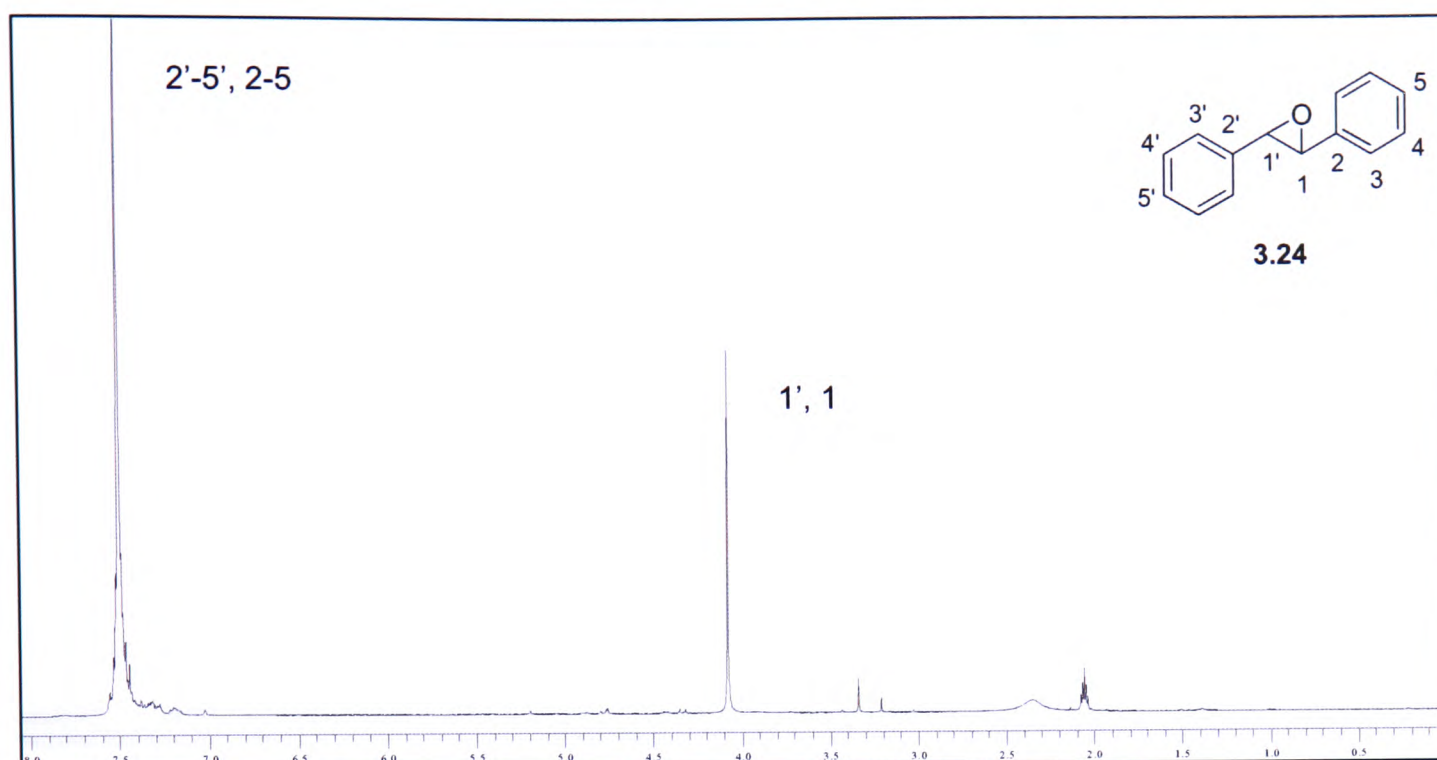


Entry	Solvent	Equiv of <b>2.18c</b>	Base	Equiv of base	Time (h)	Yield (%)	
						<b>3.24</b>	<b>3.25</b>
1	MeOH	8	KOH	3	48	62	-
2	MeOH	5	NaHCO <sub>3</sub>	5	48	30	38
3	MeOH	13	K <sub>2</sub> CO <sub>3</sub>	2	24	77	-
4	Dioxane	5	K <sub>2</sub> CO <sub>3</sub>	2	24	28	-
5	Dioxane	11	-	-	24	64	-
6	CH <sub>3</sub> CN	13	KHCO <sub>3</sub>	2	24	97	>1
7	CH <sub>3</sub> CN	10	KHCO <sub>3</sub>	3	24	98	2
8	CH <sub>3</sub> CN	10	KHCO <sub>3</sub>	6	24	86	14
9	CH <sub>3</sub> CN	15	KHCO <sub>3</sub>	10	24	91	9

<sup>a</sup>Conversion by HPLC. <sup>b</sup>Determined by  $^1\text{H-NMR}$  spectroscopy.

A range of olefins were oxidised using the following procedure: a mixture of KHCO<sub>3</sub> (2 equiv) and peracid resin **2.18c** (8 equiv) in acetonitrile at room temperature (conversion monitored by TLC and GC) for 10 hours gave the best results. After filtration of the resin and evaporation of the solvent, the corresponding oxiranes were analysed and showed highly pure products without any needing for

additional purification (Figure 3.2). Oxiranes were obtained in high conversions even for the electron poor substrates (Table 3.5, entries 2-4).

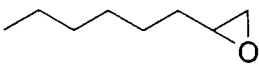
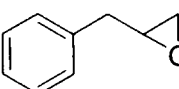
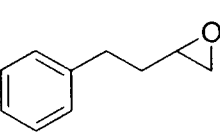
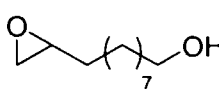
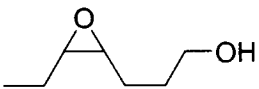
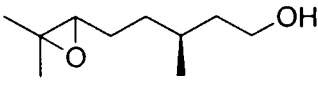


**Figure 3. 2**  $^1\text{H}$ -NMR of crude *trans*-stilbene oxide **3.25** synthesized using resin **2.18c**

A longer reaction time for citronellol **3.26g** was required, probably due to steric problems between the hindered substrate and the polymeric matrix **2.18c**.

**Table 3.5** Alkenes oxidations to epoxides using Dowex MAC-3<sup>®</sup> peracid resin **2.18c**

Entry	Product	Time (h)	Yield(%) <sup>a</sup>
1	 3.27a	8	97

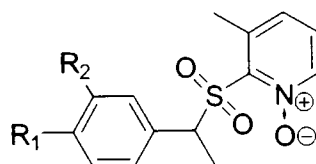
2		8	97
	<b>3.27b</b>		
3		12	97
	<b>3.27c</b>		
4		12	98
	<b>3.27d</b>		
5		24	97
	<b>3.27e</b>		
6		12	96
	<b>3.27f</b>		
7		24	96
	<b>3.27g</b>		

<sup>a</sup>Determined by <sup>1</sup>H-NMR spectroscopy.

### 3.3 Oxidations of pyridines

#### 3.3.1 Introduction

The chemistry and applications of pyridine *N*-oxides have recently gained much attention due to their usefulness as synthetic intermediates<sup>166</sup> and their biological importance. Heterocyclic pyridine *N*-oxides have also found application as a protecting groups,<sup>167</sup> oxidants,<sup>168</sup> ligands in metal complexes<sup>169</sup> and catalysts.<sup>170</sup> Recently, pyridine *N*-oxide derivatives have been reported to be inhibitory to both HIV-1 and HIV-2 replication.<sup>171</sup>



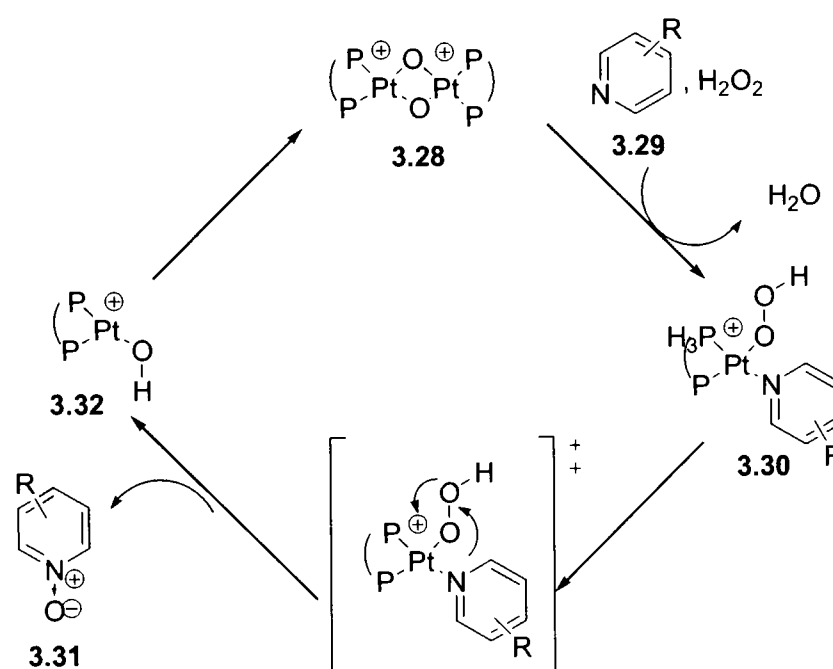
$R_1 = \text{H}, R_2 = \text{CH}_3$  **JPL-71**

$R_1 = \text{CH}_3, R_2 = \text{H}$  **JPL-78**

**Figure 3.3** Pyridine *N*-oxide derivatives as anti-HIV compounds



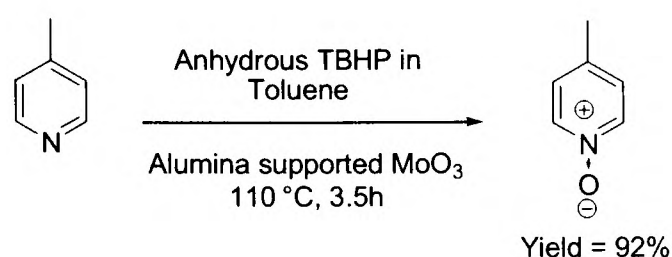
Pyridine *N*-oxides are prepared by oxidation of the corresponding pyridines, and a variety of effective oxidants have been reported in literature to accomplish this transformation, most of them suffer from drawbacks, such as the use of stoichiometric amounts of corrosive acids or toxic metallic compounds that generate copious amounts of undesirable wastes. Recently a diphosphine Pt(II) complex<sup>172</sup> was used as heterogeneous catalyst in the oxidation of pyridines **3.29** with H<sub>2</sub>O<sub>2</sub> as an oxidant. The latter oxidant was employed in stoichiometric quantities, indicating that it does not undergo parallel decomposition pathways. A possible catalytic cycle is given in Scheme 3.19.



**Scheme 3.19** Postulated mechanism for pyridine oxidation mediated by Pt(II) complex

In the first step the formation of mono-cationic hydroperoxo-amino complex **3.30** by dissociation of the dimeric-OH **3.28** structure is aided by protonation and water displacement. In the final step the products **3.31** and **3.32** are formed. Heterogeneous catalysts such as tungstate-exchanged Mg–Al layered double hydroxide (LDH-WO<sub>4</sub><sup>2-</sup>)<sup>173</sup> and zeolite supported copper<sup>174</sup> have been employed for the oxidation of pyridines. The use of heterogeneous catalysts offers several inherent advantages such as ease of recovery/recycling, safe handling, high atom economy, enhanced stability and long lifetime of the catalyst. Recently, alumina-supported MoO<sub>3</sub> in combination with anhydrous *tert*-butylhydroperoxide (TBHP) was successfully employed as a

recyclable catalyst for the oxidation of pyridine derivatives to corresponding *N*-oxides (Scheme 3.20).<sup>175</sup>



**Scheme 3.20** Oxidation of 4-picoline to the corresponding *N*-oxides using alumina supported MoO<sub>3</sub>

After completion of the reaction the catalyst was separated by filtration and recycled without significant loss of activity.

### 3.3. 2 Oxidation of pyridine derivatives by Dowex MAC-3<sup>®</sup> peracid resin

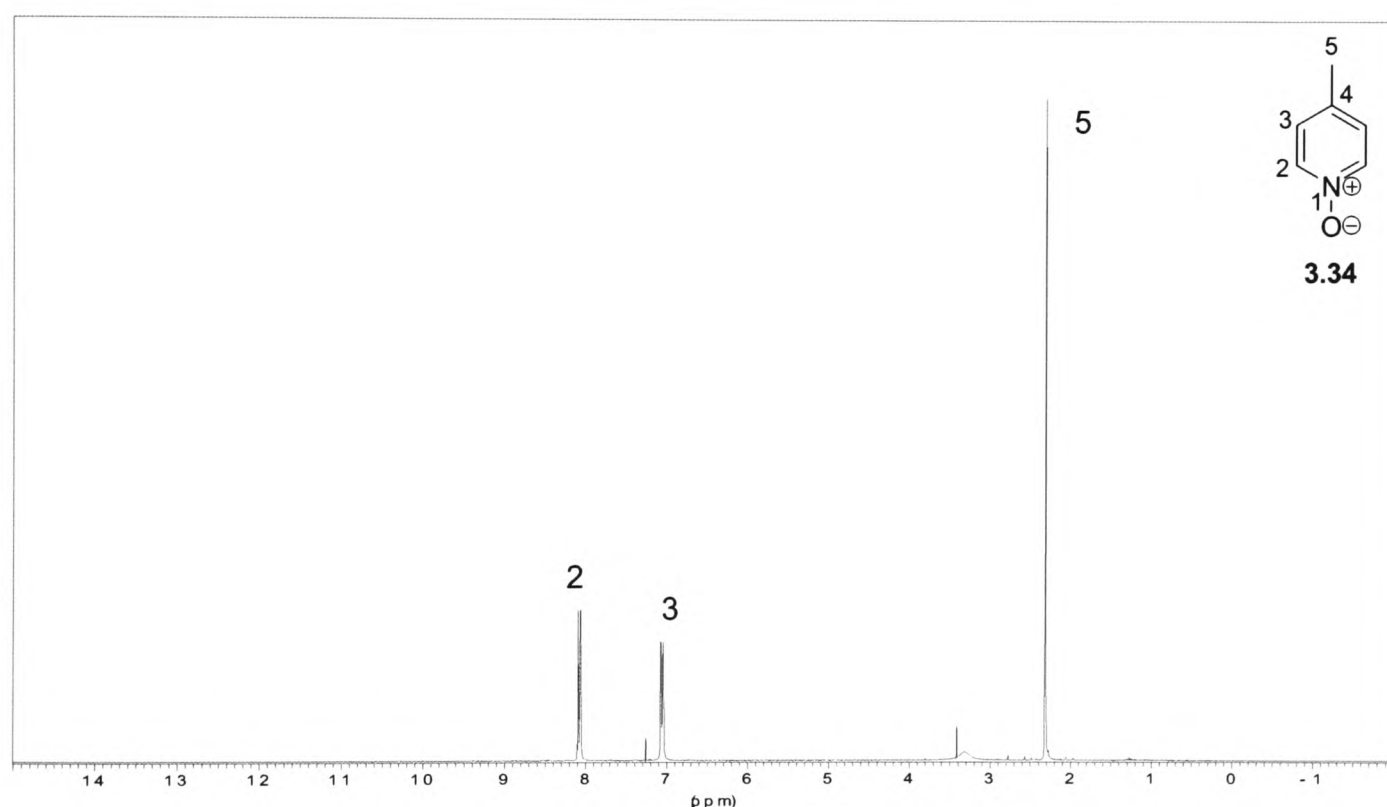
The oxidation of pyridines was investigated using peracid resin **2.18c** as an oxidant; 4-picoline **3.33** was selected as the model substrate and its oxidation was studied with different conditions to optimise the reaction. Results of these experiments are presented in Table 3.6.

**Table 3. 6** Evaluation of the optimal solvent for the oxidation of 4-picoline

Entry	Solvent	Time (h)	Yield <sup>a</sup> (%)
1	MeOH	5	> 98
2	Dioxane	6	> 98
3	CH <sub>3</sub> CN	3	> 98
4	DMF	4	> 98

<sup>a</sup>Determined by <sup>1</sup>H-NMR spectroscopy.

The effect of various additional solvents such as acetonitrile, methanol, dioxane, DMF using 10 equiv of Dowex MAC-3<sup>®</sup> peracid resin **2.18c** was investigated, and it was decided to carry on the reaction at room temperature to avoid any possible deterioration of the peracid resin. The progress of the reaction was monitored by HPLC. After completion of the reaction, the peracid resin was separated by filtration and the filtrate was concentrated to give the pure corresponding *N*-oxides, which were characterised by comparing their physical and spectral data with the literature values. At room temperature the reaction was found to proceed smoothly, especially in CH<sub>3</sub>CN (Table 3.5, entry 3), although attempts to decrease the amount of peracid resin **2.18c** led to longer reaction times and unreacted 4-picoline in the reaction mixture.



**Figure 3. 4** <sup>1</sup>H-NMR of crude 4-picoline oxide **3.34** synthesised using resin **2.18c**

To generalise the reaction, oxidation of various pyridine derivatives was conducted using 10 equiv of resin **2.18c** in acetonitrile, at room temperature. If after 16 hours the conversion was not complete, another 5 equiv of resin **2.18c** were added (Table 3.6, entry 3). Pure *N*-oxide pyridines were recovered by filtration and evaporation of the solvent (Figure 3.4).

**Table 3.7** Pyridine oxidations using Dowex MAC-3<sup>®</sup> peracid resin **2.18c**

Product	R	 3.38 <sup>a</sup>	 3.39 <sup>a</sup>	 3.40 <sup>a</sup>
<b>a</b>	-CH <sub>3</sub>	95(3)	95(3)	95(3)
<b>b</b>	-CO <sub>2</sub> Me	96(4)	98(4)	95(8)
<b>c</b>	-CN	97(4)	96(8)	96(20) <sup>a</sup>
<b>d</b>	-OMe	90(24) <sup>b</sup>	96(6)	92(24)
<b>e</b>	-Ph	97(4)	87(8)	85(20) <sup>b</sup>
<b>f</b>	-Cl	92(8) <sup>b, c</sup>	95(33) <sup>b</sup>	84(24) <sup>b</sup>
<b>g</b>	-Br	94(8) <sup>b, c</sup>	85(20) <sup>b</sup>	88(24) <sup>b</sup>
<b>h</b>	-F	-	92(4)	-

<sup>a</sup> %Yield %, reaction time (*h*) in brackets, <sup>b</sup> 15 equiv of peracid resin **2.18c**, <sup>c</sup> MeOH as solvent

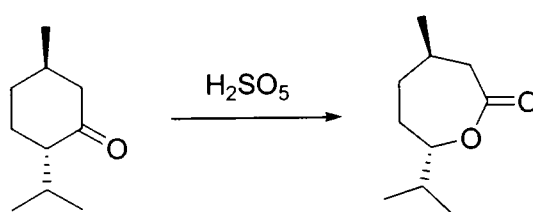


Some additional resin washings with methanol were required to recover the product in high yield. *N*-oxide products were obtained in almost quantitative yield after simple filtration (Table 3.7), however in the case of the *ortho*-substituted pyridines (**3.40c-g**) a large excess of resin was necessary, probably due to steric hindrance issues. The presence of a strong electron-donating group, such as the methoxy group in position 4 of the aromatic ring (**3.40d**), was responsible for decreasing in the rate of oxidation. The same effect was also observed for electron-withdrawing substituents but in position 3 of the aromatic ring (**3.39f, g**). In all the others cases, the reactions proceeded smoothly and in high yield at room temperature.

### 3. 4 Applications in Baeyer-Villiger oxidation

#### 3.4. 1 Introduction

The oxidation of ketones by peroxyacids was discovered by Baeyer and Villiger in 1899 when they were working on the cleavage of cyclic ketones. They reported the oxidation of menthone to the corresponding lactone (Scheme 3.21) using a mixture of sodium persulfate and concentrated sulfuric acid (Caro's acid).<sup>176</sup> Additionally, they mentioned that this new reaction works also with several small-ring ketones, but the corresponding lactones could not be isolated.<sup>177</sup>



**Scheme 3.21** Baeyer-Villiger oxidation of menthone with Caro's acid

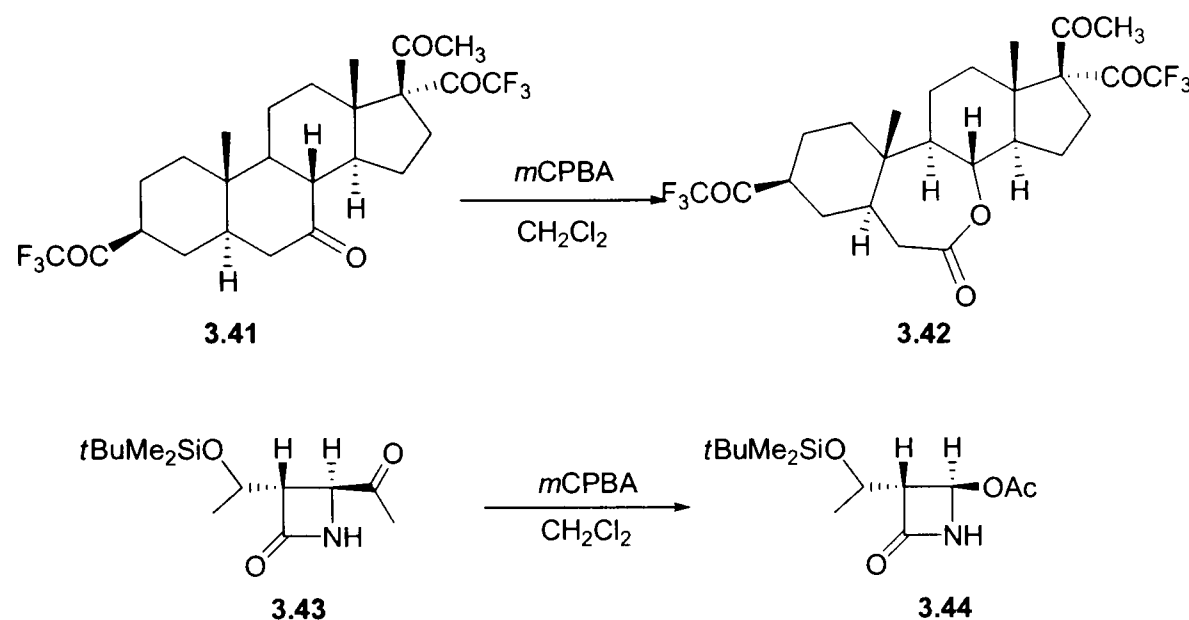
The persulfuric acid was subsequently replaced by an organic peracid, and the Baeyer-Villiger reaction became one of the most well-known and widely applied reactions in organic synthesis.<sup>178</sup> Since the discovery of the reaction, substantial progress has been made to understand the mechanism, to predict migratory preferences and to apply this conversion in preparative chemistry.<sup>179</sup> The oxidation of ketones by peroxyacids can

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offer different advantages that have made the Baeyer-Villiger oxidation a successful methodology in synthetic organic chemistry.<sup>180</sup>

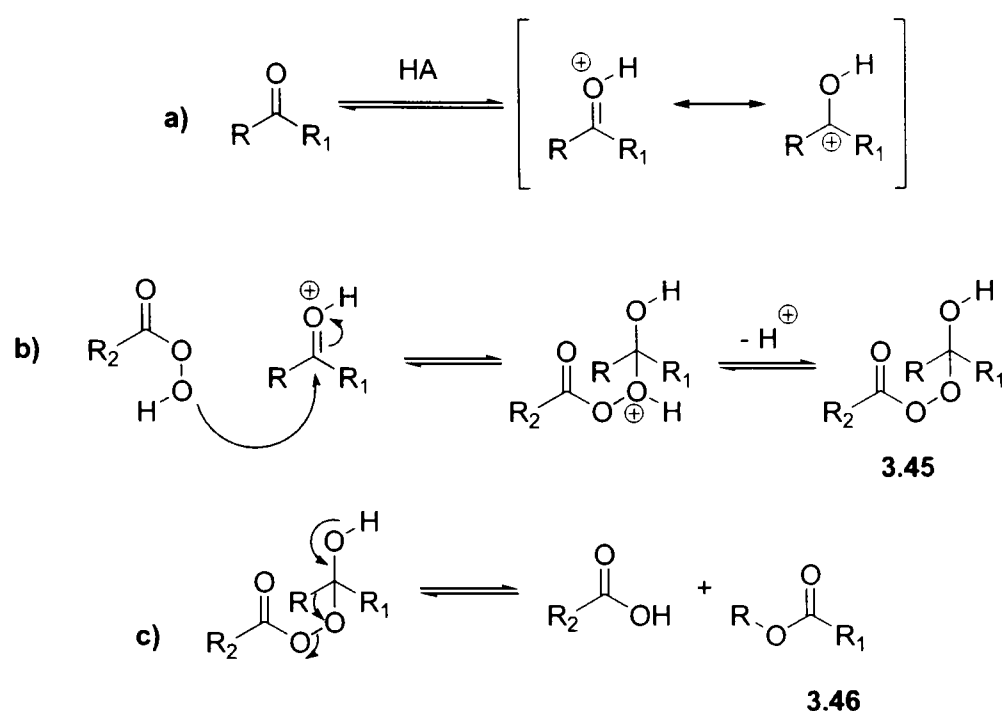
- A variety of carbonyl compounds can be oxidised; for example, ketones are converted into esters, cyclic ketones into lactones, benzaldehydes into phenols, or carboxylic acids and  $\alpha$ -diketones into anhydrides.
- The general reactions conditions are compatible with the presence of many functional groups.
- The regiochemistry of the reaction can normally be predicted using the scale of migratory aptitude for different groups as a reference.
- It is generally stereoselective, which implies that migrating chiral carbons retain their absolute configuration in the product.
- A wide variety of peroxy acids can be used as oxidants for the reaction.

Two examples that summarise the above points are shown in Scheme 3.22. Pregnan-7,20-dione **3.41**, a precursor of 7-oxyprogesterone, reacts only at the C-7 carbonyl **3.42**.<sup>181</sup> The acyl-substituted  $\beta$ -lactam **3.43**, an intermediate in the synthesis of carbapenem antibiotics, is converted exclusively into the corresponding acetate **3.44**.<sup>182</sup> Both reactions proceed almost exclusively at the carbonyl group despite the presence of other potentially oxidisable functional groups and with retention of configuration at the migrating carbon atom.



**Scheme 3.22** Application of Baeyer-Villiger oxidation for the synthesis of pharmaceutical compounds

The currently accepted general mechanism for this reaction with organic peroxides is, in its general features, based on the first mechanism proposed by Criegee.<sup>183</sup> Essentially the reaction involves two steps (Scheme 3.23 b). The first step is the addition of the peroxyacid to the carbonyl compound to form a Criegee adduct **3.45**. This step usually requires the presence of a catalyst; which can be an acid<sup>184</sup> or an enzyme<sup>185</sup> and is usually employed in a homogeneous phase with the other reagents (Scheme 3.23 a). The second step is the rearrangement of the adduct to the reaction end-product **3.46**. The overall rate of the reaction is determined by the second step, which involves the migration of an alkyl or aryl group,<sup>186</sup> which retains the stereochemistry of the migrating site.<sup>187</sup> Relative migration aptitude of different groups (*t*-alkyl > cyclohexyl > *sec*-alkyl > benzyl > phenyl > *n*-alkyl > cyclopentyl > methyl)<sup>188</sup> in the Baeyer-Villiger reaction suggested that the migrating group is carrying a partial positive charge in the transition state (anionotropic rearrangements).<sup>180</sup> Moreover, the reactivity scale of the oxidant (trifluoroperacetic acid > monopermaleic acid > mono-*o*-perphthalic acid > 3,5-dinitroperbenzoic acid > *p*-nitroperbenzoic acid > *meta*-chloroperbenzoic acid  $\approx$  performic acid > perbenzoic acid > peracetic acid  $\approx$  hydrogen peroxide > *tert*-buthylhydroperoxide) is related to the strength of the conjugate acid of the leaving group in the Criegee adduct **3.46**.



Scheme 3.23 General mechanism for Baeyer-Villiger oxidation

The Baeyer-Villiger oxidation of ketones is a reaction of major synthetic interest in organic chemistry with a large range of possible applications spanning diverse areas as the synthesis of antibiotics and steroids, the synthesis of pheromones for agrochemistry and the synthesis of monomers for polymerisation and natural products.<sup>189</sup>

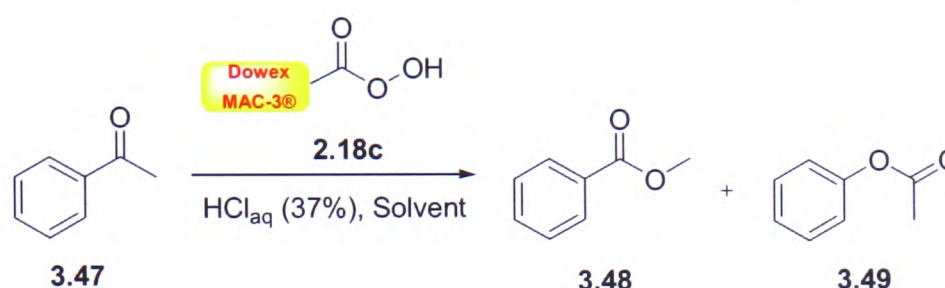
### 3.4. 2 Baeyer-Villiger oxidation using Dowex MAC-3<sup>®</sup> peracid resin

The possibility of using the peracid resin **2.18c** in the Baeyer-Villiger oxidation was examined. Preliminary work was focused on the oxidation of acetophenone. A series of experiments was carried out in order to optimise reaction conditions. In preliminary studies a solution of acetophenone in different solvents was shaken with Dowex MAC-3<sup>®</sup> peracid resin **2.18c**. In all experiments the ratio between the solvent and the amount of Dowex MAC-3<sup>®</sup> peracid resin **2.18c** was 4:1 (4 mL of solvent for 1 g of resin). The results are shown in Table 3.8. The reaction was monitored by HPLC and <sup>1</sup>H-NMR, the products were identified by comparison of their retention times and chemical shift with those of commercial samples. It was observed that, contrary to expectations, the carboxylic acid groups present on the resin were not able to efficiently catalyse the reaction. The conversion was very slow and after 4 days using 15 fold in excess of Dowex MAC-3<sup>®</sup> peracid resin **2.18c**, only 8% of the



ketone was oxidised. A second series of oxidations were carried out using hydrochloric acid as a co-catalyst. The solution of acetophenone was shaken with different amounts of  $\text{HCl}_{\text{aq}}$  (37%) and **2.18c**. The presence of  $\text{HCl}$  was able to increase the rate of the reaction, and the full conversion of the substrate was observed.

**Table 3.8** Evaluation of the optimal conditions for the oxidation of acetophenone



Entry	Solvent	Time	Equiv of $\text{HCl}_{\text{aq}}$ (37%)	Equiv of <b>2.18c</b>	Conversion <sup>a</sup> (%)	Yield <sup>b</sup> (%)	
						3.48	3.49
1	MeOH	5h	5	7	80	50	30
2	MeOH	5h	10	10	95	87	8
3	$\text{CH}_3\text{CN}$	1d	5	10	70	52	18
4	$\text{CH}_3\text{CN}$	5 h	5	10	95	90	10
5	Dioxane	1d	5	7	>98	85	15
6	Dioxane	8h	10	7	95	88	12
7	Hexane	1d	5	10	78	65	13
8	Hexane	8h	10	10	92	87	13

<sup>a</sup>Conversion by HPLC. <sup>b</sup>Determined by  $^1\text{H}$ -NMR spectroscopy.

The reaction worked in several organic solvents such as methanol, acetonitrile, 1,4-dioxane and hexane. Although, in all the examined solvents the product selectivity remained high, the best reactivity was observed in acetonitrile. In this solvent the oxidation was obtained after 5 h at room temperature, in the presence of 5 equiv of  $\text{HCl}_{\text{aq}}$  37% and 10 equiv of resin **2.18c** (Table 3.8, entry 4). In order to investigate the general applicability of our methodology a variety of cyclic and acyclic ketones

were oxidised. It was also decided to use deuterated acetonitrile as a solvent to study the oxidations directly by  $^1\text{H}$ -NMR. The identity of products was determined by comparison with authentic samples using  $^1\text{H}$ -NMR or by GC-MS analysis. The conversion and product selectivity were determined using GC analysis. The results are summarised in Table 3.9.

**Table 3. 9** Baeyer-Villiger oxidation of ketones using peracid resin **2.18c**

Entry	Ketones	Time	Conversion <sup>a</sup> (%)	Selectivity <sup>a,b</sup> (%)	
				3.51a-e	3.52a-e
1	 <b>3.50a</b>	5 h	>98	 (>95)	
2	 <b>3.50b</b>	5 h	>98	 (>93)	
3	 <b>3.50c</b>	1d	80	 (75)	 (25)
4	 <b>3.50d</b>	5 h	85	 (92)	 (8)
5	 <b>3.50e</b>	5 h	76	 (70)	 (30)

<sup>a</sup>Conversion by GC-MS. <sup>b</sup>Determined by  $^1\text{H}$ -NMR spectroscopy

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In general peracid resin **2.18c** provided good conversion and selectivity in the Baeyer–Villiger reaction at room temperature, all cyclic ketones exhibited higher conversions after 5 h of reaction; the presence of an aromatic ring adjacent to the carbonyl group was found to decrease conversion and selectivity (Table 3.9, entry 3). Finally, tests with aliphatic carbonyl compounds provided results that were also consistent with the proposed mechanism; the secondary alkyl group was showing the migration aptitude compared to competing methyl group (Table 3.9, entry 4).

### 3. 5 Conclusions

In conclusion, it has been demonstrated that the peroxycarboxylic resin described in the previous chapter showed good activity in a series of oxidation reactions (Dowex MAC-3<sup>®</sup>). Several organic substrates (sulfides, alkenes, pyridine derivatives) were oxidised using this supported reagent, and all products were isolated in high purity via simple filtration. Despite the fact that peracids are unstable compounds, the resin showed to be easy to handle, safe from any danger of explosion while used in the experiments. The ease of use in addition to the simplicity of its preparation and the high reactivity, are critical advantages that make this supported reagent ideal for a range of different applications; from the small scale laboratory synthesis to medium scale process for intermediate synthesis (flow system) due to its high favorable economic impact.

## 4. Experimental section

### 4.1 General procedures

Reaction solvents were purchased from commercial sources. Ion-exchange resins (DOWEX MAC-3<sup>®</sup>, Amberlite IRP-64<sup>®</sup>, Amberlite IRC-50<sup>®</sup>) and hydrogen peroxide (30 Wt. %, 50 Wt. %) were purchased from Aldrich. Chromatography refers to flash column chromatography and was performed on 230-400 mesh silica gel. Reactions were monitored by TLC (Merck) with detection under UV light illumination or through alkaline KMnO<sub>4</sub> oxidation. Melting points are reported uncorrected. <sup>1</sup>H- and <sup>13</sup>C-NMR spectra were recorded on a Bruker ARX 250 or AV 300 NMR; chemical shifts are quoted in ppm and *J* values given in Hz. All <sup>13</sup>C-NMR experiments were supported with a DEPT experiment. IR spectra were obtained on a Thermo Mattson Satellite FTIR spectrometer or a Bruker Tensor 27 Spectrometer, with 16 scans, at a resolution of  $\pm 4\text{ cm}^{-1}$ . The FT-IR spectrometer was fitted with a Specac single reflection diamond ATR Golden Gate, and neat compounds were used for analysis. Frequencies are reported in  $\text{cm}^{-1}$  and only frequencies corresponding to significant functional groups are reported. Abbreviations used for reporting data are s = strong, m = medium, w = weak, br = broad, bd = broad doublet. Analytical HPLC were carried out on a Hewlett Packard HP1100 Chemstation eluting with (A) 0.1% TFA/H<sub>2</sub>O and (B) 0.04% TFA/MeCN. Method: column discovery C<sub>18</sub>, 5 cm. x 4.6 mm, 5  $\mu\text{m}$ , flow rate: 1 mL/min. Gradient: 10% (B) to 90% (B) over 3 min, then 90% for 1 min. Detection by UV (220, 254 and 260 nm). GC/MS analyses were performed on a VG Trio 1000. Maspec II was used to acquire and process the GC/MS data. The following method was used: injection port temperature 250 °C; oven temperature 60 °C, 60-250 °C (15 °C/min), 40 min. Differential scanning calorimetry measurements were carried out in a Perkin Elmer apparatus. A resin sample (2-3 mg) was sealed in a high- pressure stainless steel crucible with a gold O-ring that can withstand pressures up to 2 MPa. The temperature range scanned was between 25 to 200 °C with a heating rate of 10 °C / min. HRMS analyses were performed by the Mass Spectrometry Service of the University of Southampton and the University of Edinburgh. The numbering systems adopted to assign protons and carbon signals in



the NMR spectra in some structures is different from the numbering following IUPAC nomenclature. The IUPAC names of each compound are reported in brackets.

## 4.2 General procedures chapter II

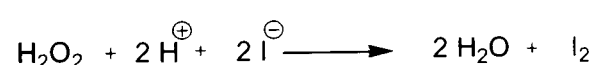
### 4.2.1 General procedure for re-generation of ion exchange resins

Commercial ion exchange resin (20 g) was washed in a soxhlet (MeOH) for 48 hours and dried under reduced pressure at 50 °C. The resin (10 g) was shaken for 20 min with 1N HCl (50 mL), after filtration the resin was washed with deionised water (2×100 mL). The resin was shaken for 20 min with 1N NaOH (50 mL). After filtration, the resin was washed with deionised water (2×100 mL). The procedure was repeated three times. The resin was stored in HCl 1N for 24 h. HCl was removed by washing with deionised water (2×100 mL), which was then removed by washing with MeOH (2×100 mL) before drying the resin beads under reduced pressure.

### 4.2.2 General procedure for oxidation of resins

An amount of resin (10 g) was treated with the corresponding acid and a 30% (or 50 %) aq solution of hydrogen peroxide at 30 °C (or 50 °C) for 6 h or 16 h. The resin was washed with MeOH until the eluent was H<sub>2</sub>O<sub>2</sub> free. A water solution of potassium iodide (0.3 mL, 0.1 N) and few drops of a solution of starch (0.1 M in water) were added to an aliquot of MeOH (5 mL) used to wash the resin: the non appearance of colour in solution indicated the absence of peroxides. The beads were dried under reduced pressure for 12 hours in the dark. An aliquot of oxidised resin (0.1 g) was tested with a ceric sulphate solution.

### 4.2.3 Determination of peroxides in solution



A water solution of potassium iodide (0.3 mL, 0.1 N) and few drops of a starch solution (0.1 M in water) were added to a solution of glacial acetic acid (3 mL) and

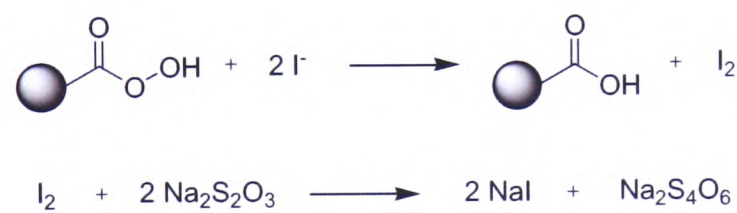
MeOH (5 mL) used to wash the resin. The mixture was stirred for 10 min at 25 °C: a colourless solution indicates the absence of peroxides.

**4.2.4 Determination of hydrogen peroxide absorbed in the resin; ceric sulfate method<sup>113</sup>**



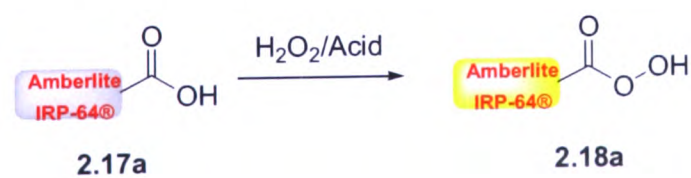
An aliquot of oxidised resin (0.1 g) was added to a water solution of cerium sulphate (3 mL, 0.1 N) and H<sub>2</sub>SO<sub>4</sub> (1 mL, 0.1 N). The mixture was stirred for 10 min at 30 °C. A colour change of the solution from orange-pink to light blue indicates the presence of hydrogen peroxide.

**4.2.5 Evaluation of oxidation capacity by iodometric titration**



Loading of the oxidised resin was evaluated by iodometric titration. The resin (200-300 mg) was added to glacial acetic acid (3 mL) and heated at 40° C. Potassium iodide (1.1 equiv of the expected loading) was added and the suspension was stirred for 30 min. The suspension was then titrated with a standard solution of 0.1 N potassium thiosulfate and starch indicator. Corrections calculated from blank determinations with the respective unoxidised resins were applied.

**4. 3 Oxidation of Amberlite IRP-64<sup>®</sup> 2.17a**



Commercial ion exchange resin Amberlite IRP-64<sup>®</sup> was regenerated using the procedure described in 4.2.1. The oxidation of the carboxylic acid groups of the resin was accomplished by reaction with hydrogen peroxide in different concentrations (30 wt. % and 50 wt. %) in the presence of sulfuric acid or a sulfonic acid at different temperatures over various times. The solutions used varied to tune the loading of the resins: 4, 10, 20 and 40 equiv. For the acid catalyst, it was decided to use: sulfuric acid, *p*-toluenesulfonic acid and methanesulfonic acid. Various quantities of acid were investigated: 1, 2 and 4 equiv based on the loading of the resin. The mixture of the resin with the acid was gently stirred for 10 min, and then the peroxide was added dropwise at room temperature. The experiments were carried out at two different temperatures (30 °C and 50 °C) and for different times: 6, 16 and 24 hours. The resins were filtered and washed with methanol, until the washing solutions were free of hydrogen peroxide. The absence of hydrogen peroxide adsorbed on the resin was determined by cerium sulphate and ferroin indicator with a ceric sulphate solution. Loading of the oxidised resin was evaluated by iodometric titration.

**Acid catalyst: H<sub>2</sub>SO<sub>4</sub> (≈18.1 M) T= 30 °C**

Time	Equiv H <sub>2</sub> O <sub>2</sub> 30 Wt. %	Oxidation capacity using 1 equiv of acid	Oxidation capacity using 2 equiv of acid	Oxidation capacity using 4 equiv of acid
6h	4	0.1	0.2	0.2
6h	10	0.1	0.2	0.2
6h	20	0.1	0.1	0.1
6h	40	0.1	0.1	0.1
16h	4	0.3	0.2	0.2
16h	10	0.2	0.3	0.2
16h	20	0.2	0.2	0.1
16h	40	0.1	0.1	0.1



Acid catalyst: *p*-toluenesulfonic acid (≈3.4 M) T= 30 °C

Time	Equiv H <sub>2</sub> O <sub>2</sub> 30 Wt. %	Oxidation capacity using 1 equiv of acid	Oxidation capacity using 2 equiv of acid	Oxidation capacity using 4 equiv of acid
6h	4	0.1	0.1	0.2
6h	10	0.1	0.2	0.2
6h	20	0.1	0.1	0.1
6h	40	0.1	0.1	0.1
16h	4	0.2	0.3	0.2
16h	10	0.2	0.2	0.2
16h	20	0.1	0.1	0.2
16h	40	0.1	0.1	0.1

Acid catalyst: methanesulfonic acid (≈15.4 M) T= 30 °C

Time	Equiv H <sub>2</sub> O <sub>2</sub> 30 Wt. %	Oxidation capacity using 1 equiv of acid	Oxidation capacity using 2 equiv of acid	Oxidation capacity using 4 equiv of acid
6h	4	0.1	0.2	0.2
6h	10	0.2	0.3	0.1
6h	20	0.1	0.2	0.1
6h	40	0.1	0.1	0.1
16h	4	0.2	0.2	0.2
16h	10	0.1	0.3	0.2
16h	20	0.2	0.2	0.1
16h	40	0.1	0.1	0.1

Acid catalyst: H<sub>2</sub>SO<sub>4</sub> (≈18.1 M) T= 50 °C

Time	Equiv H <sub>2</sub> O <sub>2</sub> 30 Wt. %	Oxidation capacity using 1 equiv of acid	Oxidation capacity using 2 equiv of acid	Oxidation capacity using 4 equiv of acid
6h	4	0.2	0.1	0.2
6h	10	0.1	0.3	0.3
6h	20	0.1	0.1	0.2
6h	40	0.1	0.1	0.1
16h	4	0.2	0.3	0.3
16h	10	0.2	0.4	0.2
16h	20	0.1	0.2	0.3
16h	40	0.1	0.1	0.1



Acid catalyst: *p*-toluenesulfonic acid (≈3.4 M) T= 50 °C

Time	Equiv H <sub>2</sub> O <sub>2</sub> 30 Wt. %	Oxidation capacity using 1 equiv of acid	Oxidation capacity using 2 equiv of acid	Oxidation capacity using 4 equiv of acid
6h	4	0.2	0.2	0.3
6h	10	0.1	0.3	0.2
6h	20	0.1	0.1	0.1
6h	40	0.1	0.1	0.1
16h	4	0.3	0.2	0.2
16h	10	0.2	0.3	0.3
16h	20	0.1	0.1	0.1
16h	40	0.1	0.1	0.1

Acid catalyst: methanesulfonic acid (≈15.4 M) T= 50 °C

Time	Equiv H <sub>2</sub> O <sub>2</sub> 30 Wt. %	Oxidation capacity using 1 equiv of acid	Oxidation capacity using 2 equiv of acid	Oxidation capacity using 4 equiv of acid
6h	4	0.2	0.3	0.2
6h	10	0.3	0.3	0.2
6h	20	0.1	0.2	0.1
6h	40	0.1	0.1	0.1
16h	4	0.3	0.2	0.3
16h	10	0.2	0.4	0.4
16h	20	0.1	0.4	0.1
16h	40	0.1	0.1	0.1

Acid catalyst: H<sub>2</sub>SO<sub>4</sub> (≈18.1 M) T= 50 °C

Time	Equiv H <sub>2</sub> O <sub>2</sub> 50 Wt. %	Oxidation capacity using 1 equiv of acid	Oxidation capacity using 2 equiv of acid	Oxidation capacity using 4 equiv of acid
6h	4	0.2	0.3	0.3
6h	10	0.2	0.3	0.2
6h	20	0.2	0.2	0.3
6h	40	0.1	0.1	0.1
16h	4	0.5	0.5	0.5
16h	10	0.4	0.7	0.5
16h	20	0.3	0.3	0.4
16h	40	0.2	0.2	0.3

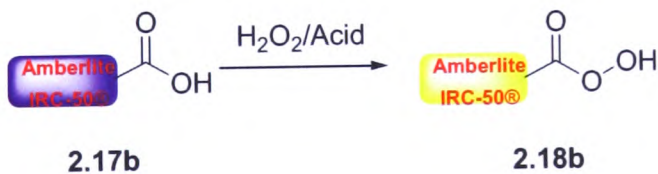
Acid catalyst: *p*-toluenesulfonic acid (≈3.4 M) T= 50 °C

Time	Equiv H <sub>2</sub> O <sub>2</sub> 50 Wt. %	Oxidation capacity using 1 equiv of acid	Oxidation capacity using 2 equiv of acid	Oxidation capacity using 4 equiv of acid
6h	4	0.2	0.2	0.2
6h	10	0.2	0.3	0.3
6h	20	0.2	0.2	0.1
6h	40	0.1	0.1	0.1
16h	4	0.4	0.5	0.4
16h	10	0.3	0.5	0.5
16h	20	0.2	0.3	0.3
16h	40	0.2	0.2	0.1

Acid catalyst: methanesulfonic acid (≈15.4 M) T= 50 °C

Time	Equiv H <sub>2</sub> O <sub>2</sub> 50 Wt. %	Oxidation capacity using 1 equiv of acid	Oxidation capacity using 2 equiv of acid	Oxidation capacity using 4 equiv of acid
6h	4	0.3	0.4	0.3
6h	10	0.2	0.5	0.4
6h	20	0.2	0.4	0.1
6h	40	0.1	0.1	0.1
16h	4	0.6	0.7	0.5
16h	10	0.4	0.6	0.6
16h	20	0.2	0.6	0.3
16h	40	0.2	0.3	0.3

4. 4 Oxidation of Amberlite IRC-50<sup>®</sup> 2.17b



The same procedure described above for Amberlite IRP-64<sup>®</sup> was followed in the attempt to oxidise Amberlite IRC-50<sup>®</sup>. The results of these experiments are shown in the tables below.



Acid catalyst: H<sub>2</sub>SO<sub>4</sub> (≈18.1 M) T= 30 °C

Time	Equiv H <sub>2</sub> O <sub>2</sub> 30 Wt. %	Oxidation capacity using 1 equiv of acid	Oxidation capacity using 2 equiv of acid	Oxidation capacity using 4 equiv of acid
6h	4	0.2	0.2	0.3
6h	10	0.2	0.3	0.2
6h	20	0.1	0.1	0.1
6h	40	0.1	0.1	0.1
16h	4	0.4	0.4	0.5
16h	10	0.3	0.6	0.5
16h	20	0.2	0.3	0.2
16h	40	0.1	0.2	0.3

Acid catalyst: *p*-toluenesulfonic acid (≈3.4 M) T= 30 °C

Time	Equiv H <sub>2</sub> O <sub>2</sub> 30 Wt. %	Oxidation capacity using 1 equiv of acid	Oxidation capacity using 2 equiv of acid	Oxidation capacity using 4 equiv of acid
6h	4	0.1	0.1	0.1
6h	10	0.1	0.2	0.2
6h	20	0.1	0.1	0.2
6h	40	0.1	0.2	0.1
16h	4	0.2	0.2	0.2
16h	10	0.2	0.4	0.2
16h	20	0.1	0.1	0.1
16h	40	0.1	0.1	0.1

Acid catalyst: methanesulfonic acid (≈15.4 M) T= 30 °C

Time	Equiv H <sub>2</sub> O <sub>2</sub> 30 Wt. %	Oxidation capacity using 1 equiv of acid	Oxidation capacity using 2 equiv of acid	Oxidation capacity using 4 equiv of acid
6h	4	0.3	0.4	0.3
6h	10	0.3	0.5	0.4
6h	20	0.2	0.2	0.2
6h	40	0.2	0.1	0.2
16h	4	0.4	0.5	0.4
16h	10	0.4	0.6	0.5
16h	20	0.3	0.3	0.4
16h	40	0.2	0.3	0.3

Acid catalyst: H<sub>2</sub>SO<sub>4</sub> (≈18.1 M) T= 50 °C

Time	Equiv H <sub>2</sub> O <sub>2</sub> 30 Wt. %	Oxidation capacity using 1 equiv of acid	Oxidation capacity using 2 equiv of acid	Oxidation capacity using 4 equiv of acid
6h	4	0.5	0.4	0.5
6h	10	0.4	0.7	0.6
6h	20	0.3	0.4	0.2
6h	40	0.2	0.3	0.3
16h	4	0.6	0.7	0.7
16h	10	0.8	0.9	0.8
16h	20	0.6	0.6	0.5
16h	40	0.3	0.3	0.2

Acid catalyst: *p*-toluenesulfonic acid (≈3.4 M) T= 50 °C

Time	Equiv H <sub>2</sub> O <sub>2</sub> 30 Wt. %	Oxidation capacity using 1 equiv of acid	Oxidation capacity using 2 equiv of acid	Oxidation capacity using 4 equiv of acid
6h	4	0.2	0.4	0.2
6h	10	0.2	0.4	0.3
6h	20	0.1	0.3	0.3
6h	40	0.1	0.2	0.2
16h	4	0.2	0.3	0.4
16h	10	0.3	0.5	0.5
16h	20	0.3	0.4	0.2
16h	40	0.2	0.2	0.2

Acid catalyst: methanesulfonic acid (≈15.4 M) T= 50 °C

Time	Equiv H <sub>2</sub> O <sub>2</sub> 30 Wt. %	Oxidation capacity using 1 equiv of acid	Oxidation capacity using 2 equiv of acid	Oxidation capacity using 4 equiv of acid
6h	4	0.4	0.6	0.7
6h	10	0.5	0.7	0.8
6h	20	0.3	0.4	0.3
6h	40	0.3	0.5	0.3
16h	4	0.4	0.8	0.8
16h	10	0.5	0.9	0.9
16h	20	0.4	0.4	0.6
16h	40	0.4	0.6	0.5



Acid catalyst: H<sub>2</sub>SO<sub>4</sub> (≈18.1 M) T= 50 °C

Time	Equiv H <sub>2</sub> O <sub>2</sub> 50 Wt. %	Oxidation capacity using 1 equiv of acid	Oxidation capacity using 2 equiv of acid	Oxidation capacity using 4 equiv of acid
6h	4	0.5	0.5	0.6
6h	10	0.4	0.7	0.6
6h	20	0.3	0.5	0.4
6h	40	0.3	0.4	0.4
16h	4	0.8	0.8	0.7
16h	10	0.7	0.9	0.6
16h	20	0.4	0.6	0.4
16h	40	0.4	0.5	0.4

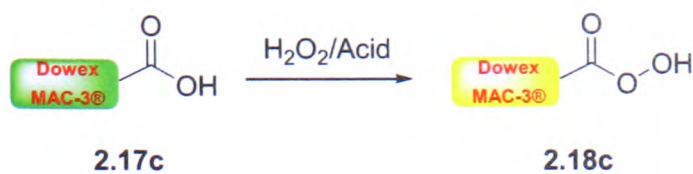
Acid catalyst: *p*-toluenesulfonic acid (≈3.4 M) T= 50 °C

Time	Equiv H <sub>2</sub> O <sub>2</sub> 50 Wt. %	Oxidation capacity using 1 equiv of acid	Oxidation capacity using 2 equiv of acid	Oxidation capacity using 4 equiv of acid
6h	4	0.4	0.5	0.4
6h	10	0.4	0.6	0.5
6h	20	0.2	0.3	0.3
6h	40	0.3	0.3	0.2
16h	4	0.5	0.6	0.4
16h	10	0.5	0.7	0.6
16h	20	0.4	0.5	0.4
16h	40	0.3	0.4	0.5

Acid catalyst: methanesulfonic acid (≈15.4 M) T= 50 °C

Time	Equiv H <sub>2</sub> O <sub>2</sub> 50 Wt. %	Oxidation capacity using 1 equiv of acid	Oxidation capacity using 2 equiv of acid	Oxidation capacity using 4 equiv of acid
6h	4	0.7	0.8	0.8
6h	10	0.5	1.1	0.9
6h	20	0.4	0.7	0.5
6h	40	0.5	0.6	0.6
16h	4	0.8	0.9	0.7
16h	10	0.9	1.2	0.8
16h	20	0.7	0.7	0.5
16h	40	0.6	0.6	0.5

4.5 Oxidation of Dowex MAC-3<sup>®</sup> 2.17c



The same procedure described above for Amberlite IRP-64<sup>®</sup> was followed in the attempt to oxidise Dowex MAC-3<sup>®</sup>. The results of these experiments are shown in the tables below.

Acid catalyst: H<sub>2</sub>SO<sub>4</sub> (≈18.1 M) T= 30 °C

Time	Equiv H <sub>2</sub> O <sub>2</sub> 30 Wt. %	Oxidation capacity using 1 equiv of acid	Oxidation capacity using 2 equiv of acid	Oxidation capacity using 4 equiv of acid
6h	4	0.8	0.9	0.8
6h	10	0.5	1.1	0.5
6h	20	0.2	0.4	0.3
6h	40	0.3	0.2	0.3
16h	4	1.7	1.6	1.5
16h	10	1.5	2.3	2.1
16h	20	1.1	1.3	1.5
16h	40	1.2	1.0	0.9

Acid catalyst: *p*-toluenesulfonic acid (≈3.4 M) T= 30 °C

Time	Equiv H <sub>2</sub> O <sub>2</sub> 30 Wt. %	Oxidation capacity using 1 equiv of acid	Oxidation capacity using 2 equiv of acid	Oxidation capacity using 4 equiv of acid
6h	4	0.5	0.6	0.4
6h	10	0.6	0.8	0.5
6h	20	0.5	0.4	0.6
6h	40	0.4	0.5	0.6
16h	4	0.7	0.8	0.8
16h	10	0.6	1.1	0.9
16h	20	0.5	0.6	0.6
16h	40	0.4	0.5	0.6



Acid catalyst: methanesulfonic acid (≈15.4 M) T= 30 °C

Time	Equiv H <sub>2</sub> O <sub>2</sub> 30 Wt. %	Oxidation capacity using 1 equiv of acid	Oxidation capacity using 2 equiv of acid	Oxidation capacity using 4 equiv of acid
6h	4	0.8	1.1	1.0
6h	10	0.9	1.5	1.3
6h	20	0.6	0.7	0.8
6h	40	0.7	0.8	0.8
16h	4	1.8	2.1	1.9
16h	10	1.7	2.1	2.1
16h	20	1.3	1.7	1.6
16h	40	1.2	1.4	1.4

Acid catalyst: H<sub>2</sub>SO<sub>4</sub> (≈18.1 M) T= 50 °C

Time	Equiv H <sub>2</sub> O <sub>2</sub> 30 Wt. %	Oxidation capacity using 1 equiv of acid	Oxidation capacity using 2 equiv of acid	Oxidation capacity using 4 equiv of acid
6h	4	2.1	2.0	1.8
6h	10	1.9	2.2	1.9
6h	20	0.8	1.0	1.1
6h	40	0.6	0.8	0.9
16h	4	3.1	3.2	2.9
16h	10	2.5	3.5	3.0
16h	20	1.7	2.2	2.5
16h	40	1.5	1.7	1.6

Acid catalyst: *p*-toluenesulfonic acid (≈3.4 M) T= 50 °C

Time	Equiv H <sub>2</sub> O <sub>2</sub> 30 Wt. %	Oxidation capacity using 1 equiv of acid	Oxidation capacity using 2 equiv of acid	Oxidation capacity using 4 equiv of acid
6h	4	0.9	1.0	1.1
6h	10	0.9	1.2	1.0
6h	20	0.5	0.9	0.7
6h	40	0.4	0.5	0.6
16h	4	1.9	1.6	1.8
16h	10	1.6	2.2	1.3
16h	20	0.9	0.9	0.7
16h	40	0.6	0.7	0.7

Acid catalyst: methanesulfonic acid (≈15.4 M) T= 50 °C

Time	Equiv H <sub>2</sub> O <sub>2</sub> 30 Wt. %	Oxidation capacity using 1 equiv of acid	Oxidation capacity using 2 equiv of acid	Oxidation capacity using 4 equiv of acid
6h	4	2.1	2.1	2.2
6h	10	1.9	2.8	2.4
6h	20	2.0	1.0	2.1
6h	40	1.7	1.8	1.9
16h	4	3.7	3.6	3.6
16h	10	3.5	4.2	4.0
16h	20	2.7	2.2	2.5
16h	40	2.2	2.5	2.6

Acid catalyst: H<sub>2</sub>SO<sub>4</sub> (≈18.1 M) T= 30 °C

Time	Equiv H <sub>2</sub> O <sub>2</sub> 50 Wt. %	Oxidation capacity using 1 equiv of acid	Oxidation capacity using 2 equiv of acid	Oxidation capacity using 4 equiv of acid
6h	4	2.3	2.2	2.1
6h	10	1.9	2.8	2.1
6h	20	0.8	1.5	1.1
6h	40	0.9	1.1	1.2
16h	4	2.9	3.1	2.9
16h	10	2.5	3.8	3.1
16h	20	2.1	2.5	2.2
16h	40	1.9	2.2	2.1

Acid catalyst: *p*-toluenesulfonic acid (≈3.4 M) T= 30 °C

Time	Equiv H <sub>2</sub> O <sub>2</sub> 50 Wt. %	Oxidation capacity using 1 equiv of acid	Oxidation capacity using 2 equiv of acid	Oxidation capacity using 4 equiv of acid
6h	4	1.0	1.1	0.9
6h	10	1.2	1.5	1.1
6h	20	0.7	0.9	0.7
6h	40	0.4	0.4	0.2
16h	4	1.8	1.9	1.8
16h	10	1.9	2.1	2.0
16h	20	1.3	1.5	1.1
16h	40	0.6	0.7	0.5



Acid catalyst: methanesulfonic acid (≈15.4 M) T= 30 °C

Time	Equiv H <sub>2</sub> O <sub>2</sub> 50 Wt. %	Oxidation capacity using 1 equiv of acid	Oxidation capacity using 2 equiv of acid	Oxidation capacity using 4 equiv of acid
6h	4	3.3	3.3	3.1
6h	10	2.5	3,8	3.2
6h	20	1.8	2.5	2.2
6h	40	2.0	2.1	2.1
16h	4	3.7	4.1	4.1
16h	10	2.5	4.7	4.2
16h	20	2.1	2.8	3.0
16h	40	2.9	2.7	2.9

Acid catalyst: H<sub>2</sub>SO<sub>4</sub> (≈18.1 M) T= 50 °C

Time	Equiv H <sub>2</sub> O <sub>2</sub> 50 Wt. %	Oxidation capacity using 1 equiv of acid	Oxidation capacity using 2 equiv of acid	Oxidation capacity using 4 equiv of acid
6h	4	3.5	3.7	3.2
6h	10	3.2	4.2	3.7
6h	20	2.7	2.2	2.5
6h	40	2.5	2.7	2.7
16h	4	5.1	5.1	5.1
16h	10	4.8	5.4	5.5
16h	20	3.5	3.7	3.5
16h	40	3.1	3.3	3.5

Acid catalyst: *p*-toluenesulfonic acid (≈3.4 M) T= 50 °C

Time	Equiv H <sub>2</sub> O <sub>2</sub> 50 Wt. %	Oxidation capacity using 1 equiv of acid	Oxidation capacity using 2 equiv of acid	Oxidation capacity using 4 equiv of acid
6h	4	2.2	2.3	2.1
6h	10	2.0	2.8	2.3
6h	20	1.3	1.9	0.8
6h	40	0.9	0.9	1.1
16h	4	3.0	2.9	2.3
16h	10	3.1	3.2	2.5
16h	20	1.9	2.2	1.8
16h	40	1.3	1.5	1.1



**Mp:** 88-90 °C.

**<sup>1</sup>H-NMR** (300 MHz, CDCl<sub>3</sub>) δ<sub>H</sub>: 7.99-7.95 (2H, m, H<sub>2</sub>); 7.68 (1H, m, H<sub>4</sub>); 7.62-7.56 (2H, m, H<sub>3</sub>); 3.07 (3H, s, H<sub>5</sub>).

**<sup>13</sup>C-NMR** (75 MHz, CDCl<sub>3</sub>) δ<sub>C</sub>: 140.7 (C<sub>1</sub>); 133.7 (C<sub>4</sub>); 129.3 (C<sub>3</sub>); 127.3 (C<sub>2</sub>); 44.3 (C<sub>5</sub>).

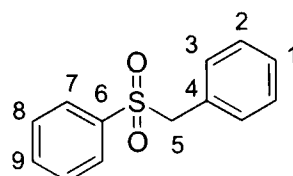
**LRMS [EI]** *m/z* (%): 156 (100); 77 (100); 51 (57).

**HPLC:** t<sub>R</sub> = 2.55 min.

**Purity (ELSD):** >98%.

The compound exhibited <sup>1</sup>H and <sup>13</sup>C-NMR spectra identical to those described previously.<sup>190</sup>

**[Methyl phenyl sulfone] 3.22a** (0.161 g, 99% yield, white solid)



**Mp:** 143-145 °C.

**<sup>1</sup>H-NMR** (300 MHz, CDCl<sub>3</sub>): δ<sub>H</sub> 7.66-7.57 (3H, m, H<sub>7</sub>, 9); 7.48-7.42 (2H, m, H<sub>8</sub>); 7.35-7.23 (3H, m, H<sub>1,3</sub>); 7.10-7.07 (2H, m, H<sub>2</sub>); 4.31 (2H, s, H<sub>5</sub>)

**<sup>13</sup>C-NMR** (75 MHz, CDCl<sub>3</sub>): δ<sub>C</sub> 137.9 (C<sub>6</sub>); 133.7 (C<sub>9</sub>); 130.8 (C<sub>4</sub>); 128.9 (C<sub>8</sub>); 128.7 (C<sub>3</sub>); 128.6 (C<sub>2</sub>); 128.6 (C<sub>7</sub>); 128.2 (C<sub>1</sub>); 62.9 (C<sub>5</sub>).

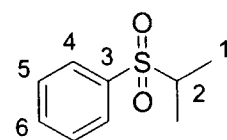
**LRMS [EI]** *m/z* (%): 232 (100); 91 (100); 77 (13); 51 (19).

**HPLC:** t<sub>R</sub> = 3.65 min.

**Purity (ELSD):** >98%.

The compound exhibited <sup>1</sup>H and <sup>13</sup>C-NMR spectra identical to those described previously.<sup>191</sup>

**[Isopropyl phenyl sulfone] 3.22b** (0.128 g, 99% yield, colourless oil)



**<sup>1</sup>H-NMR** (300 MHz, CDCl<sub>3</sub>): δ<sub>H</sub> 7.90-7.86 (2H, m, H<sub>4</sub>); 7.65(1H, m, H<sub>6</sub>); 7.59-7.53 (2H, m, H<sub>5</sub>); 3.18 (1H, heptet, *J* = 6.8 Hz, H<sub>2</sub>); 1.28 (6H, d, *J* = 6.8 Hz, H<sub>1</sub>).

**<sup>13</sup>C-NMR** (75 MHz, CDCl<sub>3</sub>): δ<sub>C</sub> 137.0 (C<sub>3</sub>); 133.6 (C<sub>6</sub>); 129.0 (C<sub>5</sub>); 129.0 (C<sub>4</sub>); 55.6 (C<sub>2</sub>); 15.7 (C<sub>1</sub>).

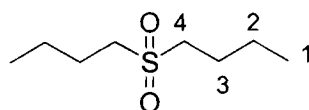
**LRMS [EI]** *m/z* (%): 184 (100); 143 (25); 77 (93); 51 (57), 43 (83).

**HPLC:** *t<sub>R</sub>* = 3.22 min.

**Purity (ELSD):** >98%.

The compound exhibited <sup>1</sup>H and <sup>13</sup>C-NMR spectra identical to those described previously.<sup>192</sup>

**[Dibutyl sulfone] 3.22c** (0.123 g, 99% yield, white solid)



**Mp:** 44-46 °C.

**<sup>1</sup>H-NMR** (300 MHz, CDCl<sub>3</sub>): δ<sub>H</sub> 2.97-2.91 (4H, m, H<sub>4</sub>); 1.87-1.77 (4H, m, H<sub>3</sub>); 1.48 (4H, sextuplet, *J* = 7.5 Hz, H<sub>2</sub>); 0.96 (6H, t, *J* = 7.3 Hz, H<sub>1</sub>).

**<sup>13</sup>C-NMR** (75 MHz, CDCl<sub>3</sub>): δ<sub>C</sub> 52.5 (C<sub>4</sub>); 23.9 (C<sub>3</sub>); 21.8 (C<sub>2</sub>); 13.5 (C<sub>1</sub>).

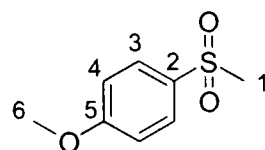
**LRMS [EI]** *m/z* (%): 123 (53); 57 (100); 41 (69).

**Purity (<sup>1</sup>H-NMR):** >98%.

The compound exhibited <sup>1</sup>H and <sup>13</sup>C-NMR spectra identical to those described previously.<sup>138</sup>



**[1-Methoxy-4-(methanesulfonyl)-benzene] 3.22d** (0.129 g, 99% yield, white solid)



**Mp:** 120-122 °C.

**<sup>1</sup>H-NMR** (300 MHz, CDCl<sub>3</sub>): δ<sub>H</sub> 7.85 (2H, d, *J* = 8.9 Hz, H<sub>3</sub>); 7.01 (2H, d, *J* = 8.9 Hz, H<sub>4</sub>); 3.88 (3H, s, H<sub>6</sub>); 3.02 (3H, s, H<sub>1</sub>).

**<sup>13</sup>C-NMR** (75 MHz, CDCl<sub>3</sub>): δ<sub>C</sub> 163.7 (C<sub>5</sub>); 132.3 (C<sub>2</sub>); 129.5 (C<sub>3</sub>); 114.5 (C<sub>4</sub>); 55.7 (C<sub>6</sub>); 44.8 (C<sub>1</sub>).

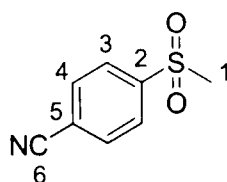
**LRMS [EI]** *m/z* (%): 186 (74); 171 (100); 77 (56); 64 (30); 51 (9).

**HPLC:** *t<sub>R</sub>* = 2.88 min.

**Purity (ELSD):** >98%.

The compound exhibited <sup>1</sup>H and <sup>13</sup>C-NMR spectra identical to those described previously.<sup>193</sup>

**[4-Methanesulfonyl-benzonitrile] 3.22e** (0.126 g, 99% yield, white solid)



**Mp:** 141-143 °C.

**<sup>1</sup>H-NMR** (300 MHz, CDCl<sub>3</sub>): δ<sub>H</sub> 8.09-8.06 (2H, m, H<sub>3</sub>); 7.90-7.86 (2H, m, H<sub>4</sub>); 3.08 (3H, s, H<sub>1</sub>).

**<sup>13</sup>C-NMR** (75 MHz, CDCl<sub>3</sub>): δ<sub>C</sub> 144.6 (C<sub>2</sub>); 133.2 (C<sub>4</sub>); 128.2 (C<sub>3</sub>); 117.7 (C<sub>5</sub>); 117.0 (C<sub>6</sub>); 44.2 (C<sub>1</sub>).

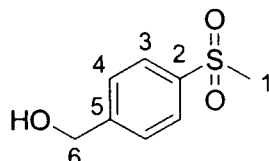
**LRMS [EI]** *m/z* (%): 181 (20); 166 (28); 119 (63); 75 (33); 63 (14); 51 (26).

**HPLC:** *t<sub>R</sub>* = 2.69 min.

**Purity (ELSD):** >98%.

The compound exhibited  $^1\text{H}$  and  $^{13}\text{C}$ -NMR spectra identical to those described previously.<sup>146</sup>

**[*p*-Methylsulfonylbenzyl alcohol] 3.22f** (0.129 g, 99% yield, white solid)



**Mp:** 84-85 °C.

**$^1\text{H}$ -NMR** (300 MHz,  $\text{CDCl}_3$ ):  $\delta_{\text{H}}$  7.85 (2H, d,  $J = 8.5$  Hz,  $\text{H}_3$ ); 7.54 (2H, d,  $J = 8.3$  Hz,  $\text{H}_4$ ); 4.78 (2H, s,  $\text{H}_6$ ); 3.02 (3H, s,  $\text{H}_1$ ).

**$^{13}\text{C}$ -NMR** (75 MHz,  $\text{CDCl}_3$ ):  $\delta_{\text{C}}$  147.4 ( $\text{C}_5$ ); 139.3 ( $\text{C}_2$ ); 127.5 ( $\text{C}_3$ ); 127.2 ( $\text{C}_4$ ); 64.1 ( $\text{C}_6$ ); 44.5 ( $\text{C}_1$ ).

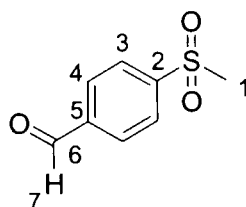
**LRMS [EI]**  $m/z$  (%): 186 (36); 171 (24); 157 (100); 77 (93); 63 (17); 51 (48); 50 (18).

**HPLC:**  $t_{\text{R}} = 1.89$  min.

**Purity (ELSD):** >98%.

The compound exhibited  $^1\text{H}$  and  $^{13}\text{C}$ -NMR spectra identical to those described previously.<sup>194</sup>

**[4-Methanesulfonyl-benzaldehyde] 3.22g** (0.127 g, 99% yield, white solid)



**Mp:** 158-159 °C.

**$^1\text{H}$ -NMR** (300 MHz,  $\text{CDCl}_3$ ):  $\delta_{\text{H}}$  10.13 (1H, s,  $\text{H}_7$ ); 8.14-8.06 (4H, m,  $\text{H}_3, 4$ ); 3.09 (3H, s,  $\text{H}_1$ ).

**$^{13}\text{C}$ -NMR** (75 MHz,  $\text{CDCl}_3$ ):  $\delta_{\text{C}}$  190.6 ( $\text{C}_6$ ); 145.4 ( $\text{C}_2$ ); 139.7 ( $\text{C}_5$ ); 130.4 ( $\text{C}_4$ ); 128.2 ( $\text{C}_3$ ); 44.3 ( $\text{C}_1$ ).

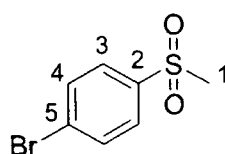
**LRMS [EI]**  $m/z$  (%): 184 (76); 169 (47); 105 (91); 77 (100); 65 (18); 51 (99).

**HPLC**:  $t_{\text{R}}$  = 2.39 min.

**Purity (ELSD)**: >98%.

The compound exhibited  $^1\text{H}$  and  $^{13}\text{C}$ -NMR spectra identical to those described previously.<sup>195</sup>

**[1-Bromomethyl-4-methanesulfonyl-benzene] 3.22h** (0.163 g, 99% yield, white solid)



**Mp**: 103-105 °C.

**$^1\text{H}$ -NMR** (300 MHz,  $\text{CDCl}_3$ ):  $\delta_{\text{H}}$  7.81 (2H, dt,  $J$  = 8.7, 2.1 Hz,  $\text{H}_3$ ); 7.71 (2H, dt,  $J$  = 8.7, 2.1 Hz,  $\text{H}_4$ ); 3.04 (3H, s,  $\text{H}_1$ ).

**$^{13}\text{C}$ -NMR** (75 MHz,  $\text{CDCl}_3$ ):  $\delta_{\text{C}}$  139.6 ( $\text{C}_2$ ); 132.7 ( $\text{C}_3$ ); 132.6 ( $\text{C}_4$ ); 129.0 ( $\text{C}_5$ ); 44.5 ( $\text{C}_1$ ).

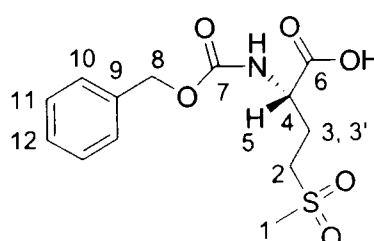
**LRMS [EI]**  $m/z$  (%): 236 (32,  $^{81}\text{Br}$ ); 234 (31,  $^{79}\text{Br}$ ); 157 (100); 155 (99); 75 (70).

**HPLC**:  $t_{\text{R}}$  = 3.30 min.

**Purity (ELSD)**: >98%.

The compound exhibited  $^1\text{H}$  and  $^{13}\text{C}$ -NMR spectra identical to those described previously.<sup>196</sup>

**[Cbz-*L*-Methionine sulfone] 3.22i** (0.218 g, 99% yield, white solid)



**Mp:** 137-138 °C.

**<sup>1</sup>H-NMR** (300 MHz, acetone d-6):  $\delta_{\text{H}}$  7.40-7.30 (5H, m, H<sub>10-12</sub>); 6.80 (1H, d,  $J$  = 8.26 Hz, NH); 5.11 (2H, s, H<sub>8</sub>); 4.44 (1H, m, H<sub>5</sub>); 3.35-3.15 (2H, m, H<sub>2</sub>); 2.97 (3H, s, H<sub>1</sub>); 2.43 (1H, m, H<sub>3</sub>); 2.22 (1H, m, H<sub>3</sub>).

**<sup>13</sup>C-NMR** (75 MHz, acetone d-6):  $\delta_{\text{C}}$  206.5 (C<sub>6</sub>); 172.9 (C<sub>7</sub>); 157.2 (C<sub>9</sub>); 138.0 (C<sub>11</sub>); 129.3 (C<sub>10</sub>); 128.7 (C<sub>12</sub>); 67.0 (C<sub>8</sub>); 53.5 (C<sub>4</sub>); 51.8 (C<sub>2</sub>); 40.7 (C<sub>1</sub>); 25.7 (C<sub>3</sub>).

**LRMS [ES<sup>-</sup>]**  $m/z$  (%): 314 (100).

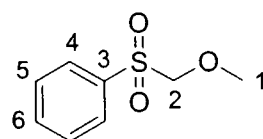
**HRMS [EI]**  $m/z$  (%): calculated for C<sub>13</sub>H<sub>17</sub>NO<sub>6</sub>S [M]<sup>+</sup> 315.0994, found 315.0946.

**HPLC:**  $t_{\text{R}}$  = 2.87 min.

**Purity (ELSD):** >98%.

The compound exhibited <sup>1</sup>H and <sup>13</sup>C-NMR spectra identical to those described previously.<sup>150</sup>

**[Phenyl methoxymethyl sulfone] 3.22j** (0.129 g, 99% yield, white solid)



**Mp:** 69-71 °C.

**<sup>1</sup>H-NMR** (300 MHz, CDCl<sub>3</sub>):  $\delta_{\text{H}}$  7.94-7.92 (2H, m, H<sub>4</sub>); 7.68 (1H, m, H<sub>6</sub>); 7.60-7.56 (2H, m, H<sub>5</sub>); 4.51 (2H, s, H<sub>2</sub>); 3.66 (3H, s, H<sub>1</sub>).

**<sup>13</sup>C-NMR** (75 MHz, CDCl<sub>3</sub>):  $\delta_{\text{C}}$  137.8 (C<sub>3</sub>); 134.5 (C<sub>6</sub>); 129.6 (C<sub>5</sub>); 129.2 (C<sub>4</sub>); 88.2 (C<sub>2</sub>); 61.6 (C<sub>1</sub>).

**LRMS [EI]**  $m/z$  (%): 125 (12); 121 (15); 91 (22); 77 (60); 51 (47); 45 (100).

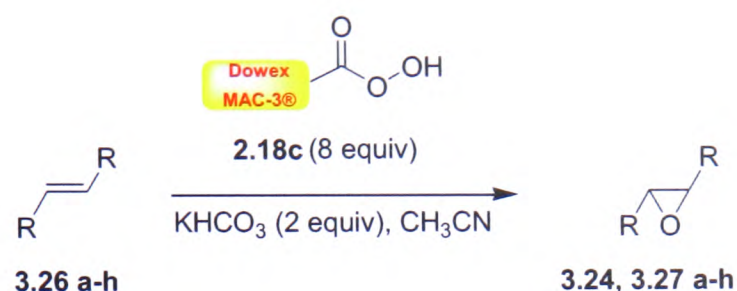
**HPLC:**  $t_{\text{R}}$  = 3.01 min.

**Purity (ELSD):** >98%.

The compound exhibited <sup>1</sup>H and <sup>13</sup>C-NMR spectra identical to those described previously.<sup>197</sup>

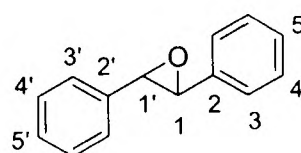


#### 4.6.2 General procedure for oxidation of alkenes to corresponding epoxides by peracid acid 2.18c



The alkene **3.26a-h** (0.7 mmol) was dissolved in  $\text{CH}_3\text{CN}$  (2 mL) and added into a stirred suspension of  $\text{KHCO}_3$  (2 equiv) and peracid resin **2.18c** (8 equiv) in  $\text{CH}_3\text{CN}$  (3 mL), at room temperature. The reaction was monitored by GC and TLC. When only the epoxide was detected, the resin was removed by filtration and washed with  $\text{CH}_3\text{CN}$  (1×25 mL) and MeOH (2×25 mL). The combined filtrates were evaporated and analysed by  $^1\text{H}$ -NMR spectroscopy without further purification.

[*Trans*-2,3-Diphenyl-oxirane] **3.24** (0.135 g, 98% yield, white solid)



**Mp:** 67-70 °C.

**$^1\text{H}$ -NMR** (300 MHz,  $\text{CDCl}_3$ ):  $\delta_{\text{H}}$  7.75-7.35 (10H, m,  $\text{H}_{3-5, 3'-5'}$ ); 4.01 (2H, s,  $\text{H}_{1, 1'}$ ).

**$^{13}\text{C}$ -NMR** (75 MHz,  $\text{CDCl}_3$ ):  $\delta_{\text{C}}$  137.2 ( $\text{C}_2, \text{C}_{2'}$ ); 128.7 ( $\text{C}_4, \text{C}_{4'}$ ); 128.4 ( $\text{C}_5, \text{C}_{5'}$ ); 125.6 ( $\text{C}_3, \text{C}_{3'}$ ); 62.9 ( $\text{C}_1, \text{C}_{1'}$ ).

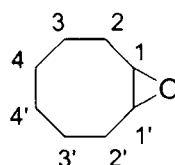
**LRMS [EI]  $m/z$  (%)**: 196 (4); 195 (100); 177 (47); 89 (40); 77 (16).

**HRMS [EI]  $m/z$** : calculated for  $\text{C}_{14}\text{H}_{12}\text{O}$  [ $\text{M}$ ] $^{+}$  196.0888, found 195.9000.

**Purity ( $^1\text{H}$ -NMR)**: >98%.

The compound exhibited  $^1\text{H}$  and  $^{13}\text{C}$ -NMR spectra identical to those described previously.<sup>198</sup>

**[cis-1,2-Epoxy-cyclooctane 3.27a** (0.085 g, 97% yield, white solid)



**Mp:** 50-52 °C.

**<sup>1</sup>H-NMR** (300 MHz, CDCl<sub>3</sub>): δ<sub>H</sub> 2.89-2.85 (2H, m, H<sub>1,1'</sub>); 2.14-2.08 (2H, m, H<sub>2,2'</sub>); 1.55-1.23 (10H, m, H<sub>2,2'-4,4'</sub>).

**<sup>13</sup>C-NMR** (75 MHz, CDCl<sub>3</sub>): δ<sub>C</sub> 55.7 (C<sub>1</sub>); 26.6 (C<sub>2</sub>); 26.4 (C<sub>4</sub>); 25.7 (C<sub>3</sub>).

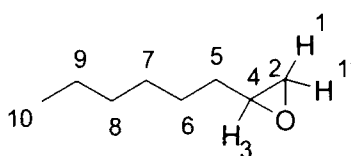
**LRMS [EI] *m/z* (%)**: 126 (2); 97 (22); 83 (27); 67 (60); 55 (100); 41 (22).

**HRMS [EI] *m/z***: calculated for C<sub>8</sub>H<sub>14</sub>O [M]<sup>+</sup> 126.1045, found 126.1040.

**Purity (<sup>1</sup>H-NMR)**: >98%.

The compound exhibited <sup>1</sup>H and <sup>13</sup>C-NMR spectra identical to those described previously.<sup>199</sup>

**[1,2-Epoxy-octane] 3.27b** (0.087 g, 97% yield, colourless oil)



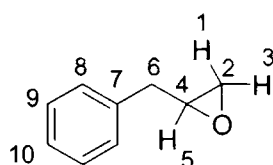
**<sup>1</sup>H-NMR** (300 MHz, CDCl<sub>3</sub>): δ<sub>H</sub> 2.89 (1H, m, H<sub>3</sub>); 2.73 (1H, dd, *J* = 5.0, 2.7 Hz, H<sub>1'</sub>), 2.46 (1H, dd, *J* = 5.0, 2.7 Hz, H<sub>1</sub>), 1.52-1.27 (10H, m, H<sub>5-9</sub>), 0.88-0.83 (3H, m, H<sub>10</sub>).

**<sup>13</sup>C-NMR** (75 MHz, CDCl<sub>3</sub>): δ<sub>C</sub> 52.6 (C<sub>4</sub>), 47.3 (C<sub>2</sub>), 32.6 (C<sub>5</sub>), 31.8 (C<sub>8</sub>); 29.2 (C<sub>7</sub>), 26.0 (C<sub>6</sub>), 22.6 (C<sub>9</sub>); 14.3 (C<sub>10</sub>).

**Purity (<sup>1</sup>H-NMR)**: >98%.

The compound exhibited <sup>1</sup>H and <sup>13</sup>C-NMR spectra identical to those described previously.<sup>200</sup>

**[1,2-Epoxy-3-phenyl-propan] 3.27c** (0.091 g, 97% yield, colourless oil)



**<sup>1</sup>H-NMR** (300 MHz, CDCl<sub>3</sub>):  $\delta_{\text{H}}$  7.37-7.23 (5H, m, H<sub>8-10</sub>); 3.17 (1H, m, H<sub>5</sub>); 2.91-2.77 (3H, m, H<sub>6</sub>, H<sub>3</sub>); 2.55 (1H, dd,  $J = 5.0, 2.6$  Hz, H<sub>1</sub>).

**<sup>13</sup>C-NMR** (75 MHz, CDCl<sub>3</sub>):  $\delta_{\text{C}}$  137.2 (C<sub>7</sub>); 129.0 (C<sub>9</sub>); 128.5 (C<sub>8</sub>); 126.6 (C<sub>10</sub>); 52.4 (C<sub>4</sub>); 46.8 (C<sub>2</sub>); 38.8 (C<sub>6</sub>).

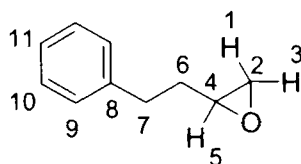
**LRMS [EI]**  $m/z$  (%): 134 (75); 105 (80); 91 (100); 77 (14).

**HRMS [EI]**  $m/z$ : calculated for C<sub>9</sub>H<sub>10</sub>O [M]<sup>+</sup> 134.0732, found 134.0732.

**Purity (<sup>1</sup>H-NMR)**: >98%.

The compound exhibited <sup>1</sup>H and <sup>13</sup>C-NMR spectra identical to those described previously.<sup>198</sup>

**[1,2-Epoxy-4-phenyl-butan] 3.27d** (0.101 g, 98% yield, colourless oil)



**<sup>1</sup>H-NMR** (300 MHz, CDCl<sub>3</sub>):  $\delta_{\text{H}}$  7.41-7.26 (5H, m, H<sub>9-11</sub>); 3.03 (1H, m, H<sub>5</sub>); 2.92-2.77 (3H, m, H<sub>6</sub>, H<sub>3</sub>); 2.54 (1H, dd,  $J = 5.0, 2.6$  Hz, H<sub>1</sub>); 1.99-1.89 (2H, m, H<sub>7</sub>).

**<sup>13</sup>C-NMR** (75 MHz, CDCl<sub>3</sub>):  $\delta_{\text{C}}$  141.7 (C<sub>8</sub>); 128.8 (C<sub>10</sub>); 128.7 (C<sub>9</sub>); 126.4 (C<sub>11</sub>); 52.1 (C<sub>4</sub>); 47.6 (C<sub>2</sub>); 34.7 (C<sub>6</sub>); 32.6 (C<sub>7</sub>).

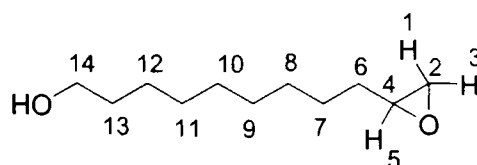
**LRMS [EI]**  $m/z$  (%): 148 (16); 131 (100); 117 (63); 91 (41).

**HRMS [EI]**  $m/z$  (%): calculated for C<sub>10</sub>H<sub>12</sub>O [M]<sup>+</sup> 148.0888, found 148.0888.

**Purity (<sup>1</sup>H-NMR)**: >98%.

The compound exhibited <sup>1</sup>H and <sup>13</sup>C-NMR spectra identical to those described previously.<sup>201</sup>

**[9-Oxiranyl-nonan-1-ol] 3.27e** (0.101 g, 97% yield, colourless oil)



**$^1\text{H-NMR}$**  (300 MHz,  $\text{CDCl}_3$ ):  $\delta_{\text{H}}$  3.60 (2H, t,  $J = 6.6$  Hz,  $\text{H}_{14}$ ); 2.91-2.85 (1H, m,  $\text{H}_3$ ), 2.74-2.70 (1H, m,  $\text{H}_5$ ); 2.44 (1H, dd,  $J = 5.0, 2.7$  Hz,  $\text{H}_1$ ); 1.71 (1H, br,  $\text{OH}$ ), 1.53-1.28 (16H, m,  $\text{H}_{6-13}$ ).

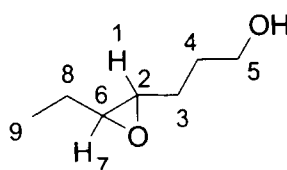
**$^{13}\text{C-NMR}$**  (75 MHz,  $\text{CDCl}_3$ ):  $\delta_{\text{C}}$  63.0 ( $\text{C}_{14}$ ); 52.5 ( $\text{C}_4$ ); 47.2 ( $\text{C}_2$ ); 32.8 ( $\text{C}_6$ ); 32.6 ( $\text{C}_{13}$ ); 29.5 ( $\text{C}_{9-11}$ ); 29.4 ( $\text{C}_8$ ); 26.0 ( $\text{C}_{12}$ ); 25.8 ( $\text{C}_7$ ).

**LRMS [EI]  $m/z$  (%)**: 187 (3); 149 (31); 95 (60); 81 (64); 41 (100).

**Purity ( $^1\text{H-NMR}$ )**: 98%.

The compound exhibited  $^1\text{H}$  and  $^{13}\text{C-NMR}$  spectra identical to those described previously.<sup>202</sup>

**[3-(3-ethyloxiran-2-yl)propan-1-ol] 3.27f** (0.0874 g, 96% yield, colourless oil)



**$^1\text{H-NMR}$**  (300 MHz,  $\text{CDCl}_3$ ):  $\delta_{\text{H}}$  3.83-3.68 (3H, m,  $\text{H}_{1,5}$ ); 3.31 (1H, m,  $\text{H}_7$ ); 1.99 (1H, bs,  $\text{OH}$ ), 1.95-1.35 (6H, m,  $\text{H}_{3,4,8}$ ); 0.98 (3H, t,  $J = 7.4$  Hz,  $\text{H}_9$ ).

**$^{13}\text{C-NMR}$**  (75 MHz,  $\text{CDCl}_3$ ):  $\delta_{\text{C}}$  82.2 ( $\text{C}_5$ ); 75.4 ( $\text{C}_6$ ); 68.2 ( $\text{C}_2$ ); 28.1 ( $\text{C}_4$ ); 26.7 ( $\text{C}_3$ ); 26.4 ( $\text{C}_8$ ); 10.2 ( $\text{C}_9$ ).

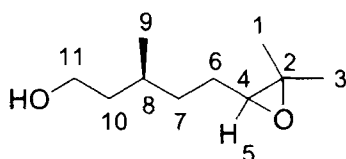
**LRMS [EI]  $m/z$  (%)**: 84 (62); 71 (100); 59 (20).

**HRMS [EI]  $m/z$  (%)**: calculated for  $\text{C}_7\text{H}_{14}\text{O}_2$  [ $\text{M}$ ]<sup>+</sup> 130.0994, found 130.0946.

**Purity ( $^1\text{H-NMR}$ )**: 95%.



**[(S)-(-)-beta-Citronellol epoxide] 3.27g** (0.116 g, 96% yield, colourless oil)



**<sup>1</sup>H-NMR** (300 MHz, CDCl<sub>3</sub>): δ<sub>H</sub> 3.76-3.61 (2H, m, H<sub>11</sub>); 2.70 (1H, t, *J* = 5.8 Hz, H<sub>5</sub>); 1.68-1.26 (13H, m, H<sub>1,3,6-10</sub>); 0.92 (3H, d, *J* = 6.2 Hz, H<sub>9</sub>).

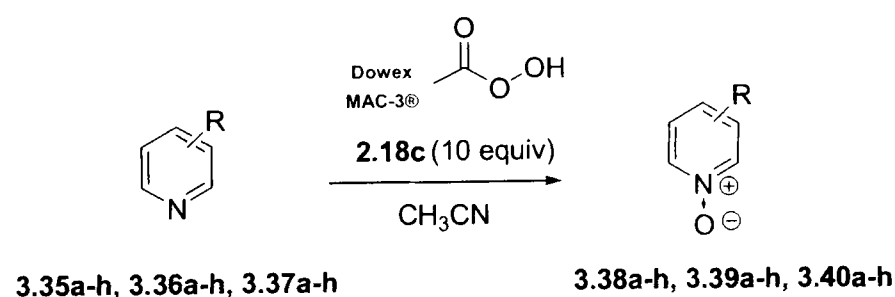
**<sup>13</sup>C-NMR** (75 MHz, CDCl<sub>3</sub>): δ<sub>C</sub> 64.8 (C<sub>4</sub>); 61.1 (C<sub>11</sub>); 40.0 (C<sub>2</sub>); 39.7 (C<sub>10</sub>); 33.9 (C<sub>7</sub>); 33.8 (C<sub>8</sub>); 29.6 (C<sub>6</sub>); 29.4 (C<sub>1</sub>); 26.6 (C<sub>3</sub>); 19.8 (C<sub>9</sub>).

**LRMS [EI] *m/z* (%)**: 87 (52); 85 (74); 71 (90); 57 (93); 43 (100).

**Purity (<sup>1</sup>H-NMR)**: 95%.

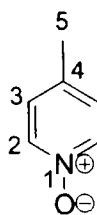
The compound exhibited <sup>1</sup>H-NMR and <sup>13</sup>C-NMR spectra identical to those previously reported.<sup>203</sup>

#### 4.6.3 General procedure for oxidation of pyridine derivatives to corresponding *N*-oxides by peracid resin **2.18c**



The pyridine derivative (1.0 mmol) was dissolved in CH<sub>3</sub>CN (2 mL) and added into a stirred suspension of peracid resin **2.18c** (10 equiv) in CH<sub>3</sub>CN (3 mL). The reaction was monitored by MS [ES<sup>+</sup>]. When only the *N*-oxide was detected, the resin was removed by filtration and washed with CH<sub>3</sub>CN (1×25 mL) and after with MeOH (3×25 mL). The combined filtrates were evaporated and analysed by <sup>1</sup>H-NMR spectroscopy without further purification.

**[4-Picoline-*N*-oxide] 3.38a** (0.103 g, 95% yield, white solid)



**Mp:** 179-182 °C.

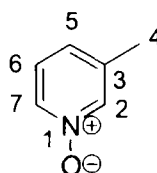
**<sup>1</sup>H-NMR** (300 MHz, CDCl<sub>3</sub>): δ<sub>H</sub> 8.11 (2H, d, *J* = 6.8 Hz, H<sub>2</sub>); 7.08 (2H, d, *J* = 6.5 Hz, H<sub>3</sub>); 2.35 (3H, s, H<sub>5</sub>).

**<sup>13</sup>C-NMR** (75 MHz, CDCl<sub>3</sub>): δ<sub>C</sub> 138.7 (C<sub>2</sub>); 137.8 (C<sub>4</sub>); 126.7 (C<sub>3</sub>); 20.3 (C<sub>5</sub>).

**LRMS [ES+]** *m/z* (%): 110.1 (100).

The compound exhibited <sup>1</sup>H-NMR and <sup>13</sup>C-NMR spectra identical to those previously reported.<sup>204</sup>

**[3-Picoline-*N*-oxide] 3.39a** (0.103 g, 95% yield, white solid)



**Mp:** 33-36 °C.

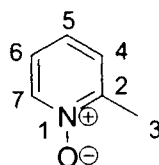
**<sup>1</sup>H-NMR** (300 MHz, CDCl<sub>3</sub>): δ<sub>H</sub> 8.11-8.02 (2H, m, H<sub>2,7</sub>); 7.21-7.07 (2H, m, H<sub>5,6</sub>); 2.27 (3H, s, H<sub>4</sub>).

**<sup>13</sup>C-NMR** (75 MHz, CDCl<sub>3</sub>): δ<sub>C</sub> 139.3 (C<sub>2</sub>); 136.9 (C<sub>3</sub>); 136.6 (C<sub>7</sub>); 127.6 (C<sub>5</sub>); 125.4 (C<sub>6</sub>); 18.3 (C<sub>4</sub>).

**LRMS [ES+]** *m/z* (%): 110.1 (100).

The compound exhibited <sup>1</sup>H-NMR and <sup>13</sup>C-NMR spectra identical to those previously reported.<sup>204</sup>

**[2-Picoline-*N*-oxide] 3.40a** (0.103 g, 95% yield, colourless oil)



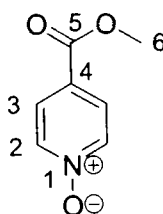
**<sup>1</sup>H-NMR** (300 MHz, CDCl<sub>3</sub>): δ<sub>H</sub> 8.28 (1H, m, H<sub>7</sub>); 7.32-7.09 (3H, m, H<sub>4-6</sub>); 2.51 (3H, s, H<sub>3</sub>).

**<sup>13</sup>C-NMR** (75 MHz, CDCl<sub>3</sub>): δ<sub>C</sub> 149.2 (C<sub>2</sub>); 139.5 (C<sub>7</sub>); 126.5 (C<sub>4</sub>); 125.9 (C<sub>5</sub>); 123.6 (C<sub>6</sub>); 17.8 (C<sub>3</sub>).

**LRMS [ES<sup>+</sup>]** *m/z* (%): 110.1.

The compound exhibited <sup>1</sup>H-NMR and <sup>13</sup>C-NMR spectra identical to those previously reported.<sup>204</sup>

**[Methyl isonicotinate-*N*-oxide] 3.38b** (0.147 g, 96% yield, white solid)



**Mp:** 117-120 °C.

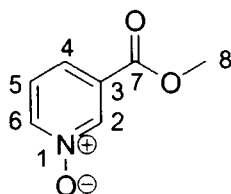
**<sup>1</sup>H-NMR** (300 MHz, DMSO): δ<sub>H</sub> 8.39-8.24 (2H, m, H<sub>2</sub>); 7.92-7.76 (2H, m, H<sub>3</sub>); 3.85 (3H, s, H<sub>6</sub>).

**<sup>13</sup>C-NMR** (75 MHz, DMSO): δ<sub>C</sub> 163.6 (C<sub>5</sub>); 139.4 (C<sub>2</sub>); 126.3 (C<sub>4</sub>); 124.9 (C<sub>3</sub>); 52.5 (C<sub>6</sub>).

**LRMS [ES<sup>+</sup>]** *m/z* (%): 154.1 (100).

The compound exhibited <sup>1</sup>H-NMR and <sup>13</sup>C-NMR spectra identical to those previously reported.<sup>204</sup>

**[Methyl nicotinate-*N*-oxide] 3.39b** (0.150 g, 98% white solid)



**Mp:** 100-102 °C.

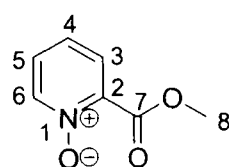
**<sup>1</sup>H-NMR** (300 MHz, DMSO):  $\delta_{\text{H}}$  8.50 (1H, m, H<sub>2</sub>); 8.44 (1H, m, H<sub>6</sub>); 7.77 (1H, m, H<sub>4</sub>); 7.56 (1H, dd,  $J = 7.8, 6.6$  Hz, H<sub>5</sub>); 3.88 (1H, s, H<sub>8</sub>)

**<sup>13</sup>C-NMR** (75 MHz, DMSO):  $\delta_{\text{C}}$  163.2 (C<sub>7</sub>); 142.4 (C<sub>2</sub>); 138.7 (C<sub>6</sub>); 129.3 (C<sub>3</sub>); 126.7 (C<sub>4</sub>); 125.2 (C<sub>5</sub>); 52.9 (C<sub>8</sub>).

**LRMS [ES+]**  $m/z$  (%): 154.1 (100).

The compound exhibited <sup>1</sup>H-NMR and <sup>13</sup>C-NMR spectra identical to those previously reported.<sup>204</sup>

**[Methyl picolinate-*N*-oxide] 3.40b** (0.145 g, 95% white solid)



**Mp:** 72-74 °C.

**<sup>1</sup>H-NMR** (300 MHz, CDCl<sub>3</sub>):  $\delta_{\text{H}}$  8.22 (1H, m, H<sub>6</sub>); 7.58 (1H, m, H<sub>3</sub>); 7.36-7.23 (2H, m, H<sub>4-5</sub>); 3.96 (3H, s, H<sub>8</sub>).

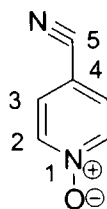
**<sup>13</sup>C-NMR** (75 MHz, CDCl<sub>3</sub>):  $\delta_{\text{C}}$  161.9 (C<sub>7</sub>); 142.0 (C<sub>2</sub>); 141.5 (C<sub>6</sub>); 127.4 (C<sub>3</sub>); 126.8 (C<sub>4</sub>); 124.7 (C<sub>5</sub>); 53.2 (C<sub>8</sub>).

**LRMS [ES+]**  $m/z$  (%): 154.1 (100).

The compound exhibited <sup>1</sup>H-NMR and <sup>13</sup>C-NMR spectra identical to those previously reported.<sup>205</sup>



**[4-Cyanopyridine-*N*-oxide] 3.38c** (0.116 g, 97% white solid)



**Mp:** 220-222 °C.

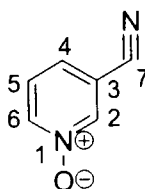
**<sup>1</sup>H-NMR** (300 MHz, CDCl<sub>3</sub>): δ<sub>H</sub> 8.40 (2H, m, H<sub>2</sub>); 7.93 (2H, m, H<sub>3</sub>).

**<sup>13</sup>C-NMR** (75 MHz, CDCl<sub>3</sub>): δ<sub>C</sub> 139.9 (C<sub>2</sub>); 126.6 (C<sub>3</sub>); 116.5 (C<sub>5</sub>); 106.2 (C<sub>4</sub>).

**LRMS [ES+]** *m/z* (%): 121.1 (100).

The compound exhibited <sup>1</sup>H-NMR and <sup>13</sup>C-NMR spectra identical to those previously reported.<sup>204</sup>

**[3-Cyanopyridine-*N*-oxide] 3.39c** (0.115 g, 96% white solid)



**Mp:** 173-176 °C.

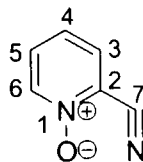
**<sup>1</sup>H-NMR** (300 MHz, CDCl<sub>3</sub>): δ<sub>H</sub> 8.90 (1H, m, H<sub>2</sub>); 8.50 (1H, m, H<sub>6</sub>); 7.82 (1H, d, *J* = 7.8 Hz, H<sub>4</sub>); 7.6 (1H, t, *J* = 7.8 Hz, H<sub>5</sub>).

**<sup>13</sup>C-NMR** (75 MHz, CDCl<sub>3</sub>): δ<sub>C</sub> 142.7 (C<sub>2</sub>); 141.1 (C<sub>6</sub>); 127.8 (C<sub>4</sub>); 126.9 (C<sub>5</sub>); 114.4 (C<sub>7</sub>); 111.5 (C<sub>3</sub>).

**LRMS [ES+]** *m/z* (%): 121.1 (100).

The compound exhibited <sup>1</sup>H-NMR and <sup>13</sup>C-NMR spectra identical to those previously reported.<sup>204</sup>

**[2-Cyanopyridine-*N*-oxide] 3.40c** (0.115 g, 96% white solid)



**Mp:** 118-120 °C.

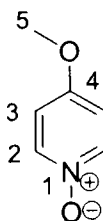
**<sup>1</sup>H-NMR** (300 MHz, CDCl<sub>3</sub>): δ<sub>H</sub> 8.85 (1H, d, *J* = 6.6 Hz, H<sub>6</sub>); 8.48 (1H, dd, *J* = 8.0, 2.0 Hz, H<sub>3</sub>); 7.81 (1H, m, H<sub>5</sub>); 7.6 (1H, m, H<sub>4</sub>).

**<sup>13</sup>C-NMR** (75 MHz, CDCl<sub>3</sub>): δ<sub>C</sub> 143.0 (C<sub>6</sub>); 141.4 (C<sub>3</sub>); 128.2 (C<sub>4</sub>); 127.3 (C<sub>5</sub>); 114.8 (C<sub>2</sub>); 111.8 (C<sub>7</sub>).

**LRMS [ES<sup>+</sup>]** *m/z* (%): 121.1 (100).

The compound exhibited <sup>1</sup>H-NMR and <sup>13</sup>C-NMR spectra identical to those previously reported.<sup>204</sup>

**[4-Methoxypyridine-*N*-oxide] 3.38d** (0.112 g, 90% white solid)



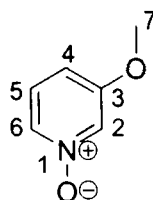
**Mp:** 88-90 °C.

**<sup>1</sup>H-NMR** (300 MHz, CDCl<sub>3</sub>): δ<sub>H</sub> 8.39-8.24 (2H, m, H<sub>2</sub>); 7.92-7.76 (2H, m, H<sub>3</sub>); 3.85 (3H, s, H<sub>5</sub>).

**<sup>13</sup>C-NMR** (75 MHz, CDCl<sub>3</sub>): δ<sub>C</sub> 163.6 (C<sub>4</sub>); 139.4 (C<sub>2</sub>); 126.3 (C<sub>3</sub>); 52.5 (C<sub>5</sub>).

**LRMS [ES<sup>+</sup>]** *m/z* (%): 126.1 (100).

The compound exhibited <sup>1</sup>H-NMR and <sup>13</sup>C-NMR spectra identical to those previously reported.<sup>204</sup>

**[3-Methoxypyridine-*N*-oxide] 3.39d** (0.121 g, 96% white solid)

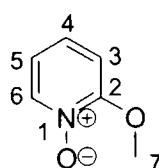
**Mp:** 99-101 °C.

**<sup>1</sup>H-NMR** (300 MHz, CDCl<sub>3</sub>): δ<sub>H</sub> 8.10 (1H, m, H<sub>2</sub>); 7.89 (1H, ddd, *J* = 6.4, 1.8, 0.6 Hz, H<sub>6</sub>); 7.15 (1H, dd, *J* = 8.6, 6.4 Hz, H<sub>5</sub>); 6.87 (1H, ddd, *J* = 8.6, 1.8, 0.6 Hz, H<sub>4</sub>); 3.88 (3H, s, H<sub>7</sub>).

**<sup>13</sup>C-NMR** (75 MHz, CDCl<sub>3</sub>): δ<sub>C</sub> 158.4 (C<sub>3</sub>); 132.8 (C<sub>6</sub>); 128.1 (C<sub>2</sub>); 125.8 (C<sub>5</sub>); 113.8 (C<sub>4</sub>); 56.5 (C<sub>7</sub>).

**LRMS [ES+]** *m/z* (%): 126.1 (100).

The compound exhibited <sup>1</sup>H-NMR and <sup>13</sup>C-NMR spectra identical to those previously reported.<sup>206</sup>

**[2-Methoxypyridine-*N*-oxide] 3.40d** (0.115 g, 92% white solid)

**Mp:** 77-80 °C.

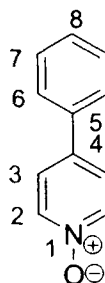
**<sup>1</sup>H-NMR** (300 MHz, CDCl<sub>3</sub>): δ<sub>H</sub> 8.24 (1H, dd, *J* = 6.5, 1.6 Hz, H<sub>6</sub>); 7.38 (1H, ddd, *J* = 8.4, 7.5, 1.6 Hz, H<sub>4</sub>); 7.22 (1H, dd, *J* = 8.4, 1.8 Hz, H<sub>3</sub>); 7.03 (1H, ddd, *J* = 7.5, 6.5, 1.8 Hz, H<sub>5</sub>); 3.69 (1H, s, H<sub>7</sub>).

**<sup>13</sup>C-NMR** (75 MHz, CDCl<sub>3</sub>): δ<sub>C</sub> 158.2 (C<sub>2</sub>); 139.4 (C<sub>6</sub>); 127.4 (C<sub>4</sub>); 117.9 (C<sub>3</sub>); 109.2 (C<sub>5</sub>); 57.0 (C<sub>7</sub>).

**LRMS [ES+]** *m/z* (%): 126.1 (100).

The compound exhibited <sup>1</sup>H-NMR and <sup>13</sup>C-NMR spectra identical to those previously reported.<sup>206</sup>

**[4-Phenylpyridine-*N*-oxide] 3.38e** (0.165 g, 97% white solid)



**Mp:** 148-150 °C.

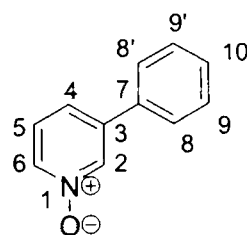
**<sup>1</sup>H-NMR** (300 MHz, CDCl<sub>3</sub>): δ<sub>H</sub> 8.29-8.24 (2H, m, H<sub>2</sub>); 7.79-7.74 (4H, m, H<sub>3,6</sub>); 7.53-7.38 (3H, m, H<sub>7,8</sub>).

**<sup>13</sup>C-NMR** (75 MHz, CDCl<sub>3</sub>): δ<sub>C</sub> 138.8 (C<sub>4</sub>); 135.9 (C<sub>2</sub>); 135.5 (C<sub>5</sub>); 129.1 (C<sub>7</sub>); 128.6 (C<sub>8</sub>); 126.1 (C<sub>6</sub>); 123.5 (C<sub>3</sub>).

**LRMS [ES+]** *m/z* (%): 172.1 (100).

The compound exhibited <sup>1</sup>H-NMR and <sup>13</sup>C-NMR spectra identical to those previously reported.<sup>207</sup>

**[3-Phenylpyridine-*N*-oxide] 3.39e** (0.148 g, 87% white solid)



**Mp:** 119-121 °C.

**<sup>1</sup>H-NMR** (300 MHz, CDCl<sub>3</sub>): δ<sub>H</sub> 8.46 (1H, bs, H<sub>2</sub>); 8.19 (1H, bd, *J*= 6.4 Hz, H<sub>6</sub>); 7.54-7.40 (6H, m, H<sub>4-5,8,8',9,9'</sub>); 7.31 (1H, m, H<sub>10</sub>).

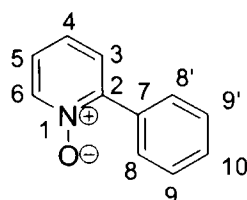
**<sup>13</sup>C-NMR** (75 MHz, CDCl<sub>3</sub>): δ<sub>C</sub> 138.0 (C<sub>2,6</sub>); 129.7 (C<sub>9,9',10</sub>); 127.3 (C<sub>3,7</sub>); 126.3 (C<sub>8,8'</sub>); 125.2 (C<sub>4</sub>); 124.6 (C<sub>5</sub>).

**LRMS [ES+]** *m/z* (%): 172.1 (100).

The compound exhibited <sup>1</sup>H-NMR and <sup>13</sup>C-NMR spectra identical to those previously reported.<sup>208</sup>



**[2-Phenylpyridine-*N*-oxide] 3.40e** (0.145 g, 85% white solid)



**Mp:** 153-155 °C.

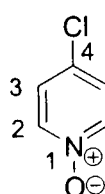
**<sup>1</sup>H-NMR** (300 MHz, CD<sub>3</sub>OD): δ<sub>H</sub> 8.22 (1H, m, H<sub>6</sub>); 7.58 (2H, m, H<sub>8</sub>, 8'); 7.36-7.23 (2H, m, H<sub>9</sub>, 9'); 7.16 (4H, m, H<sub>3-5,10</sub>).

**<sup>13</sup>C-NMR** (75 MHz, CD<sub>3</sub>OD): δ<sub>C</sub> 151.9 (C<sub>2</sub>); 142.0 (C<sub>7</sub>); 134.0 (C<sub>9</sub>, 9'); 131.4 (C<sub>10</sub>); 131.3 (C<sub>6</sub>); 130.9 (C<sub>8</sub>, 8'); 129.8 (C<sub>4</sub>); 127.8 (C<sub>3</sub>); 127.2 (C<sub>5</sub>).

**LRMS [ES+]** *m/z* (%): 172.1 (100).

The compound exhibited <sup>1</sup>H-NMR and <sup>13</sup>C-NMR spectra identical to those previously reported.<sup>209</sup>

**[4-Chloropyridine-*N*-oxide] 3.38f** (0.118 g, 92% white solid)



**Mp:** 188-190 °C.

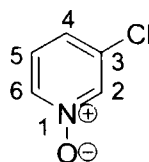
**<sup>1</sup>H-NMR** (300 MHz, DMSO): δ<sub>H</sub> 8.45-8.36 (2H, m, H<sub>2</sub>); 7.97-7.89 (2H, m, H<sub>3</sub>).

**<sup>13</sup>C-NMR** (75 MHz, DMSO): δ<sub>C</sub> 139.9 (C<sub>2</sub>); 129.6 (C<sub>3</sub>); 116.5 (C<sub>4</sub>).

**LRMS [ES+]** *m/z* (%): 130.1 (100).

The compound exhibited <sup>1</sup>H-NMR and <sup>13</sup>C-NMR spectra identical to those previously reported.<sup>204</sup>

**[3-Chloropyridine-*N*-oxide] 3.39f** (0.122 g, 95% white solid)



**Mp:** 55-57 °C.

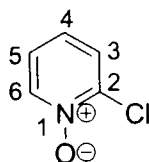
**<sup>1</sup>H-NMR** (300 MHz, CDCl<sub>3</sub>): δ<sub>H</sub> 8.26 (1H, m, H<sub>2</sub>); 8.13 (1H, m, H<sub>6</sub>); 7.44-7.32 (2H, m, H<sub>4,5</sub>).

**<sup>13</sup>C-NMR** (75 MHz, CDCl<sub>3</sub>): δ<sub>C</sub> 138.8 (C<sub>2</sub>); 137.7 (C<sub>6</sub>); 133.4 (C<sub>4</sub>); 126.3 (C<sub>3</sub>); 125.8 (C<sub>5</sub>).

**LRMS [ES+]** *m/z* (%): 130.1 (100).

The compound exhibited <sup>1</sup>H-NMR and <sup>13</sup>C-NMR spectra identical to those previously reported.<sup>204</sup>

**[2-Chloropyridine-*N*-oxide] 3.40f** (0.108 g, 84% white solid)



**Mp:** 69-70 °C.

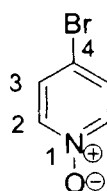
**<sup>1</sup>H-NMR** (300 MHz, CDCl<sub>3</sub>): δ<sub>H</sub> 8.28 (1H, m, H<sub>6</sub>); 7.32-7.09 (3H, m, H<sub>3-5</sub>).

**<sup>13</sup>C-NMR** (75 MHz, DMSO): δ<sub>C</sub> 149.2 (C<sub>6</sub>); 139.5 (C<sub>2</sub>); 126.5 (C<sub>3</sub>); 123.6 (C<sub>4</sub>); 117.8 (C<sub>5</sub>).

**LRMS [ES+]** *m/z* (%): 130.1 (100).

The compound exhibited <sup>1</sup>H-NMR and <sup>13</sup>C-NMR spectra identical to those previously reported.<sup>204</sup>

**[4-Bromopyridine-*N*-oxide]** 3.38g (0.162 g, 94% white solid)



**Mp:** 138-140 °C.

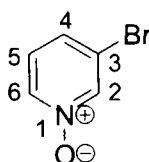
**<sup>1</sup>H-NMR** (300 MHz, DMSO):  $\delta_{\text{H}}$  8.45-8.36 (2H, m, H<sub>2</sub>); 7.97-7.89 (2H, m, H<sub>3</sub>).

**<sup>13</sup>C-NMR** (75 MHz, DMSO):  $\delta_{\text{C}}$  139.9 (C<sub>2</sub>); 129.6 (C<sub>3</sub>); 116.5 (C<sub>4</sub>).

**LRMS [ES<sup>+</sup>]**  $m/z$  (%): 174.1 (100).

The compound exhibited <sup>1</sup>H-NMR and <sup>13</sup>C-NMR spectra identical to those previously reported.<sup>210</sup>

**[3-Bromopyridine-*N*-oxide]** 3.39g (0.147 g, 85% white solid)



**Mp:** 52-55 °C.

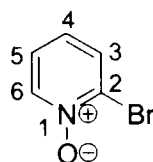
**<sup>1</sup>H-NMR** (300 MHz, DMSO):  $\delta_{\text{H}}$  8.87 (1H, m, H<sub>2</sub>); 8.48 (1H, ddd,  $J = 6.6, 1.8, 0.9$  Hz, H<sub>6</sub>); 7.82 (1H, ddd,  $J = 7.9, 1.0, 0.9$  Hz, H<sub>4</sub>); 7.59 (1H, dd,  $J = 8.6, 6.4$  Hz, H<sub>5</sub>).

**<sup>13</sup>C-NMR** (75 MHz, DMSO):  $\delta_{\text{C}}$  142.7 (C<sub>2</sub>); 141.1 (C<sub>6</sub>); 127.8 (C<sub>4</sub>); 126.9 (C<sub>3</sub>); 114.4 (C<sub>5</sub>).

**LRMS [ES<sup>+</sup>]**  $m/z$  (%): 174.1 (100).

The compound exhibited <sup>1</sup>H-NMR and <sup>13</sup>C-NMR spectra identical to those previously reported.<sup>204</sup>

**[2-Bromopyridine-*N*-oxide]** 3.40g (0.152 g, 88% white solid)



**Mp:** 58-60 °C.

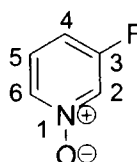
**<sup>1</sup>H-NMR** (300 MHz, CDCl<sub>3</sub>): δ<sub>H</sub> 8.28 (1H, m, H<sub>6</sub>); 7.32-7.09 (3H, m, H<sub>3-5</sub>).

**<sup>13</sup>C-NMR** (75 MHz, DMSO): δ<sub>C</sub> 149.2 (C<sub>6</sub>); 139.5 (C<sub>2</sub>); 126.5 (C<sub>3</sub>); 123.6 (C<sub>4</sub>); 117.8 (C<sub>5</sub>).

**LRMS [ES+]** *m/z* (%): 174.1 (100).

The compound exhibited <sup>1</sup>H-NMR and <sup>13</sup>C-NMR spectra identical to those previously reported.<sup>210</sup>

**[3-Fluoropyridine-*N*-oxide]** 3.39h (0.104 g, 92% white solid)



**Mp:** 62-65 °C.

**<sup>1</sup>H-NMR** (300 MHz, CDCl<sub>3</sub>): δ<sub>H</sub> 8.52 (1H, m, H<sub>2</sub>); 8.14 (1H, m, H<sub>6</sub>); 7.47 (1H, m, H<sub>4</sub>); 7.36 (1H, m, H<sub>5</sub>).

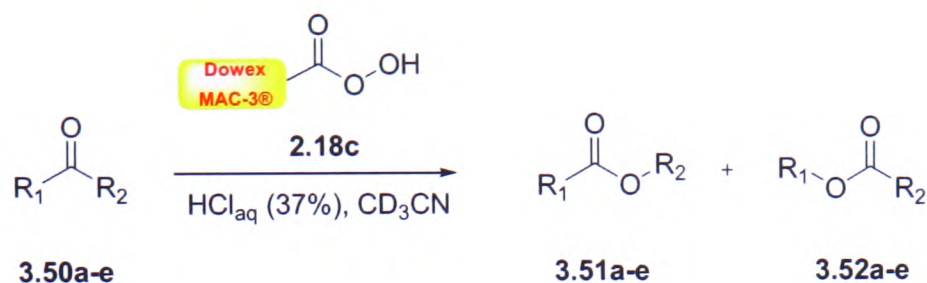
**<sup>13</sup>C-NMR** (75 MHz, CDCl<sub>3</sub>): δ<sub>C</sub> 160.6 (C<sub>3</sub>); 136.5 (C<sub>6</sub>); 129.0 (C<sub>2</sub>); 126.5 (C<sub>5</sub>); 113.1 (C<sub>4</sub>).

**LRMS [ES+]** *m/z* (%): 114.1 (100).

The compound exhibited <sup>1</sup>H-NMR and <sup>13</sup>C-NMR spectra identical to those previously reported.<sup>204</sup>

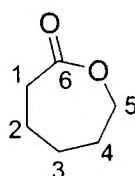


#### 4.6.4 General procedure for Baeyer-Villiger oxidation by peracid resin 2.18c



The ketone (1.0 mmol) was dissolved in a solution of CD<sub>3</sub>CN (3 mL) and HCl<sub>aq</sub> 37% (5 equiv). The solution was added into a suspension of peroxy-acid resin **2.18c** (10 equiv) in CD<sub>3</sub>CN (3 mL). Formation of products and consumption of substrates were monitored by GC-MS and <sup>1</sup>H-NMR. The identity of products was determined by comparison with authentic samples using <sup>1</sup>H-NMR or by GC-MS analysis. The conversion and product selectivity were determined using GC-MS analysis.

**$\epsilon$ -Caprolactone 3.41a** (0.108 g, 95%, pale yellow oil)



**<sup>1</sup>H-NMR** (300 MHz, CDCl<sub>3</sub>): δ<sub>H</sub> 4.35-4.23 (2H, m, H<sub>5</sub>); 3.93-3.87 (2H, m, H<sub>1</sub>); 2.12-2.81 (6H, m, H<sub>2-4</sub>).

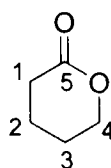
**<sup>13</sup>C-NMR** (75 MHz, CDCl<sub>3</sub>): δ<sub>C</sub> 176.2 (C<sub>6</sub>); 69.4 (C<sub>5</sub>); 34.5 (C<sub>1</sub>); 29.3 (C<sub>3</sub>); 28.7 (C<sub>4</sub>); 23.1 (C<sub>2</sub>).

**LRMS [EI]**  $m/z$  (%): 114 (20); 84 (44); 70 (21); 55 (96); 42 (100).

**Purity (GC-MS):** >95%.

The compound exhibited  $^1\text{H}$  and  $^{13}\text{C}$ -NMR spectra identical to those described previously.<sup>211</sup>

**$\delta$ -Valerolactone 3.41b** (0.093 g, 93%, pale yellow oil)



**$^1\text{H-NMR}$**  (300 MHz,  $\text{CDCl}_3$ ):  $\delta_{\text{H}}$  4.41-4.28 (2H, m,  $\text{H}_4$ ); 2.752.22 (2H, m,  $\text{H}_1$ ); 2.17-1.70 (4H, m,  $\text{H}_2$ ,  $\text{H}_3$ ).

**$^{13}\text{C-NMR}$**  (75 MHz,  $\text{CDCl}_3$ ):  $\delta_{\text{C}}$  171.7 ( $\text{C}_5$ ); 69.8 ( $\text{C}_4$ ); 30.2 ( $\text{C}_1$ ); 22.4 ( $\text{C}_3$ ); 19.2 ( $\text{C}_2$ ).

**LRMS [EI]**  $m/z$  (%): 100 (23); 56 (76); 42 (99); 41 (100); 28 (30).

**Purity (GC-MS):** >93%.

The compound exhibited  $^1\text{H}$  and  $^{13}\text{C-NMR}$  spectra identical to those described previously.<sup>212</sup>

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